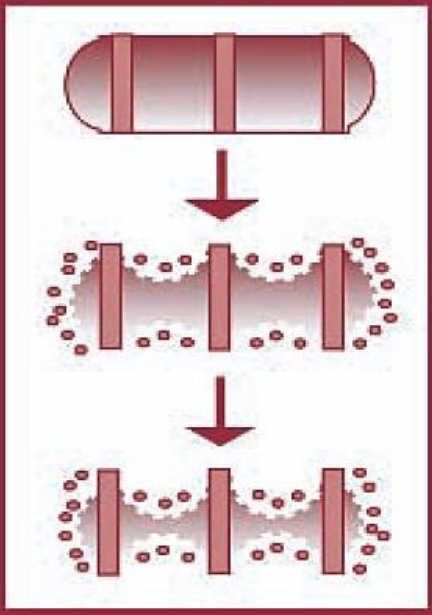
VISIT…

DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 126

Modified-Release Drug Delivery Technology



edited by
Michael J. Rathbone
Jonathan Hadgraft
Michael S. Roberts

Modified-Release Drug Delivery Technology

edited by

Michael J. Rathbone
InterAg
Hamilton, New Zealand

Jonathan Hadgraft
Medway Sciences, NRI
University of Greenwich
Chatham, England

Michael S. Roberts
Princess Alexandria Hospital
and University of Queensland
Brisbane, Queensland, Australia

Marcel Dekker, Inc. New York · Basel

Copyright © 2002 by Marcel Dekker, Inc. All Rights Reserved.

Copyright © 2003 Marcel Dekker, Inc.

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress.

ISBN: 0-8247-0869-5

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-260-6300; fax: 41-61-260-6333

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Copyright © 2003 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Copyright © 2003 Marcel Dekker, Inc.

To my daughter Jenna

—*M.J.R.*

Copyright © 2003 Marcel Dekker, Inc.

Preface

For over 50 years, interest has been expressed in optimizing drug therapy through delivery system design. For many years this revolved around incorporating drugs into erodible or inert polymers, which then acted as platforms for controlled release, an approach that has been well reviewed in the literature. In more recent times there has been a move away from simply formulating drugs into erodible or inert polymers toward the design and development of more advanced drug delivery systems that utilize sophisticated designs and manufacturing techniques and rely on novel means for controlling the release of drug from the delivery system. Over the last few decades, rapid developments have occurred in this area and we have witnessed the evolution of commercially successful companies that specialize in the design, development, and commercialization of specific (in-house) modified-release drug delivery systems.

This is an exciting and growing area of pharmaceutical research. However, to date no single volume provides detailed and specific information on even a handful of individual modified-release drug delivery systems. Therefore, we decided to edit a book comprised of chapters that collectively address this void and provide an insight into the various approaches currently adopted to achieve modified-release drug delivery.

The book is divided into parts, each of which addresses a particular route for drug delivery. Although it is assumed that the reader is already familiar with fundamental controlled-release theories, each part opens with an overview of the anatomical, physiological, and pharmaceutical challenges in formulating a modified-release drug delivery technology for each route for drug delivery. The

Copyright © 2003 Marcel Dekker, Inc.

chapters in each part provide examples of the different approaches that have been taken to design and develop an innovative modified-release drug delivery system. Each chapter presents a detailed account of a specific modified-release drug delivery technology, written by experts on that technology.

Our challenge in editing this book was that no single volume could be expected to describe every modified-release drug delivery technology currently marketed or under development. This is because of the vast and evolving nature of the area, and the lack of availability of the innovators to write a monograph on their particular technology, due to either time constraints or the proprietary nature of their work. Instead of using this as an excuse to reject the challenge, we set ourselves the aim to provide in the book as many examples of modified-release drug delivery technologies as possible.

Susan Charman and Bill Charman were the leaders of the first part of the book, which is devoted to the oral route. The Charmans provide an excellent overview of the challenges of this popular route for modified-release durg delivery. Their introduction is followed by 15 chapters that provide an insight into the novel and innovative approaches that have been taken for this route for drug delivery. These range from novel manipulations of tableting technologies (including geometric designs and osmotically driven technologies) through three-dimensional printing to the use of lipids. The second part, led by Professor Clive Wilson, discusses several diverse approaches that may be used to deliver compounds to the colon. Chapters demonstrating the innovativeness of workers in this field complement an incisive introduction that highlights the unique challenges associated with this site of absorption. The leader of Part III, Bernard Plazonnet, includes in his introduction a thorough review of currently available and emerging modified-release ophthalmic drug delivery systems. Since most of these systems are in the developmental stage and have not yet reached the commercial stage, this part contains only three chapters on specific technologies. Part IV focuses on the oral cavity as a site of drug delivery. The part leader, Professor Ian Kellaway, together with invited coauthors, provides an overview of the issues relating to the development of modified-release drug delivery systems for this route. The associated chapters highlight technologies developed for specific regions of the oral cavity, including sublingual, buccal cavity, gingiva, and periodontal pocket.

A diverse range of technology approaches are associated with the dermal and transdermal route. Part leader Professor Jonathan Hadgraft not only has written a thorough overview but has also organized a series of chapters that cover a wide range of diverse technologies from wound dressings to sprays, to propulsion of solid drug particles into the skin by means of a high-speed gas flow, to patches that deliver drugs via diffusion, iontophoresis, sonophoresis, or microprojections. The sixth part of this book addresses implant and injection technologies. In their introduction, part leaders Franklin Okumu and Jeffrey Cleland offer a comprehen-

Copyright © 2003 Marcel Dekker, Inc.

sive overview of this evolving and challenging area of drug delivery. They complement their efforts with chapters that cover a diverse range of technologies. Part VII, compiled by leaders Daniel Wermeling and Jodi Miller, offers a revealing look into the nasal route of drug delivery. Professor David Woolfson, leader of Part VIII, presents a comprehensive account of the biological and pharmaceutical challenges to the vaginal route of drug delivery, which is restricted to 50% of the population and is limited by cultural and societal constraints. The chapters dealing with this route provide an insight into the different approaches that can be employed to deliver drugs via the vaginal passage.

In Part IX Igor Gonda provides an informative overivew of the unique challenges in delivering via the pulmonary tract. This part contains chapters describing various systems, devices, formulations, and methods of delivery of drugs to the lung. It differs somewhat from other parts in the book in that the focus of pulmonary drug delivery systems is not on the control of release of the medicaments once they are deposited within the respiratory tract (although some chapters in this part do describe such approaches) but on the ability of inhalation systems to deliver drugs practically instantaneously to the target organ that is the "release" part of therapeutic activity for many of the currently approved products for inhalation. Numerous technological approaches are described in the chapters in this part, each of which provides descriptive comments on the complexity of this route for drug delivery. In the final part of this book the regulatory issues pertaining to these diverse and often complex drug delivery systems are addressed by Patrick Marroum of the United States Food and Drug Administration, who provides a regulatory overview for one of the most highly legalistic markets.

We would like to express our thanks to each of the part leaders, who spent so much time identifying technologies, communicating with contributors, writing informative overviews, and editing the chapters. We also thank all the chapter authors. Their individual innovative research activities have contributed greatly to the current modified-release drug delivery technology portfolio that exists today within the pharmaceutical industry. We are grateful to them for taking the time to share their experiences and work. Finally, we wish to express our sincere thanks to Dr. Colin Ogle. We are indebted to Colin for giving up so much of his spare time to proofread final drafts and offer many constructive suggestions for improvement of this volume.

Michael J. Rathbone
Jonathan Hadgraft
Michael S. Roberts

Copyright © 2003 Marcel Dekker, Inc.

Contents

Preface *v*
Contributors *xvii*

Part I: Oral

1. Oral Modified-Release Delivery Systems 1
Susan A. Charman and William N. Charman

2. TIMERx Oral Controlled-Release Drug Delivery System 11
Troy W. McCall, Anand R. Baichwal, and John N. Staniforth

3. MASRx and COSRx Sustained-Release Technology 21
Syed A. Altaf and David R. Friend

4. Procise: Drug Delivery Systems Based on Geometric Configuration 35
Sham K. Chopra

5. RingCap Technology 49
David A. Dickason and George P. Grandolfi

Copyright © 2003 Marcel Dekker, Inc.

6. Smartrix System: Design Characteristics and Release Properties of a Novel Erosion-Controlled Oral Delivery System 59
Horst G. Zerbe and Markus Krumme

7. TheriForm Technology 77
Charles W. Rowe, Chen-Chao Wang, and Donald C. Monkhouse

8. Accudep Technology for Oral Modified Drug Release 89
S. S. Chrai, David R. Friend, G. Kupperblatt, R. Murari, Jackie Butler, T. Francis, Araz A. Raoof, and Brian McKenna

9. Osmotically Controlled Tablets 101
Patrick S. L. Wong, Suneel K. Gupta, and Barbara E. Stewart

10. Three-Phase Pharmaceutical Form—THREEFORM—with Controlled Release of Amorphous Active Ingredient for Once-Daily Administration 115
Janez Kerč

11. Two Concepts, One Technology: Controlled-Release and Solid Dispersions with Meltrex 125
Jörg Breitenbach and Jon Lewis

12. DissoCubes—A Novel Formulation for Poorly Soluble and Poorly Bioavailable Drugs 135
Rainer H. Müller, Claudia Jacobs, and Oliver Kayser

13. IDD Technology: Oral Delivery of Water-Insoluble Drugs Using Phospholipid Stabilized Microparticulate IDD Formulations 151
Awadhesh K. Mishra, Michael G. Vachon, Pol-Henri Guivarc'h, Robert A. Snow, and Gary W. Pace

14. Liquid-Filled and -Sealed Hard Gelatin Capsule Technologies 177
Ewart T. Cole

15. The Zydis Oral Fast-Dissolving Dosage Form 191
Patrick Kearney

16. Orasolv and Durasolv: Efficient Technologies for the Production of Orally Disintegrating Tablets 203
S. Indiran Pather, Rajendra K. Khankari, and Derek V. Moe

Copyright © 2003 Marcel Dekker, Inc.

Part II: Colonic

17. Colonic Drug Delivery 217
Clive G. Wilson

18. Enteric Coating for Colonic Delivery 223
Gour Mukherji and Clive G. Wilson

19. Biopolymers and Colonic Delivery 233
Gour Mukherji and Clive G. Wilson

20. Time-Dependent Systems for Colonic Delivery 243
Wang Wang Lee, Gour Mukherji, and Clive G. Wilson

21. New Approaches for Optimizing Oral Drug Delivery: Zero-Order Sustained Release to Pulsatile Immediate Release Using the Port System 249
John R. Crison, Michael L. Vieira, and Gordon L. Amidon

22. Pulsincap and Hydrophilic Sandwich (HS) Capsules: Innovative Time-Delayed Oral Drug Delivery Technologies 257
Howard N. E. Stevens

23. Development of the Egalet Technology 263
Daniel Bar-Shalom, Lillian Slot, Wang Wang Lee, and Clive G. Wilson

24. The Enterion Capsule 273
David V. Prior, Alyson L. Connor, and Ian R. Wilding

Part III: Ocular

25. Ophthalmic Drug Delivery 289
Bernard Plazonnet

26. Ion Exchange Resin Technology for Ophthalmic Applications 315
R. Jani and E. Rhone

27. New Ophthalmic Delivery System (NODS) 329
L. Sesha Rao

Copyright © 2003 Marcel Dekker, Inc.

28. Bioadhesive Ophthalmic Drug Inserts (BODI) 341
Olivia Felt-Baeyens and R. Gurny

Part IV: Oral Mucosal

29. Oral Mucosal Drug Delivery 349
Ian W. Kellaway, Gilles Ponchel, and D. Duchêne

30. Slowly Disintegrating Buccal Mucoadhesive Plain-Tablet (S-DBMP-T) and Buccal Covered-Tablet System (BCTS) 365
Katsumi Iga

31. The Oral PowderJect Device for Mucosal Drug Delivery 381
George Costigan and Brian John Bellhouse

32. The Periochip 391
Wilfred Aubrey Soskolne

33. Polysaccharide-Based Mucoadhesive Buccal Tablets 401
Hemant H. Alur, Ashim K. Mitra, and Thomas P. Johnston

34. Medicated Chewing Gum 419
Margrethe Rømer Rassing and Jette Jacobsen

35. Immediate-Immediate Release (I^2R) Lingual or Buccal Spray Formulations for Transmucosal Delivery of Drug Substances 431
Harry A. Dugger III, Kenneth E. Cleaver, and Donald P. Cox

36. Liquid Crystalline Phases of Glyceryl Mono-oleate as Oral Mucosal Drug Delivery Systems 447
Jaehwi Lee and Ian W. Kellaway

37. Microparticles as Delivery Systems for Local Delivery to the Oral Cavity 453
Rita Cortesi, E. Menegatti, Claudio Nastruzzi, and Elisabetta Esposito

38. OraVescent: A Novel Technology for the Transmucosal Delivery of Drugs 463
S. Indiran Pather, Rajendra K. Khankari, and John M. Siebert

Copyright © 2003 Marcel Dekker, Inc.

Part V: Dermal and Transdermal

39. Dermal and Transdermal Delivery 471
Jonathan Hadgraft

40. D-TRANS Technology 481
Rama Padmanabhan, Robert M. Gale, J. Bradley Phipps, William W. van Osdol, and Wendy Young

41. E-TRANS Technology 499
J. Bradley Phipps, Rama Padmanabhan, Wendy Young, Rodney M. Panos and Anne E. Chester

42. Microfabricated Microneedles for Transdermal Drug Delivery 513
Mark R. Prausnitz, Donald E. Ackley, and J. Richard Gyory

43. Metered-Dose Transdermal Spray (MDTS) 523
Timothy M. Morgan, Barry L. Reed, and Barrie C. Finnin

44. Transfersomes: Innovative Transdermal Drug Carriers 533
Gregor Cevc

45. Advances in Wound Healing 547
Michael Walker

46. Ultrasound-Mediated Transdermal Drug Delivery 561
Samir Mitragotri and Joseph Kost

47. SLN and Lipopearls for Topical Delivery of Active Compounds and Controlled Release 571
Rainer Helmut Müller and Sylvia Wissing

48. Macroflux Technology for Transdermal Delivery of Therapeutic Proteins and Vaccines 589
Michel Cormier and Peter E. Daddona

49. Needle-Free Drug Delivery 599
Franklin Pass and John Hayes

50. Dermal PowderJect Device 607
Brian John Bellhouse and Mark A. F. Kendall

Copyright © 2003 Marcel Dekker, Inc.

51. Intraject: Prefilled, Disposable, Needle-Free Injection of Liquid Drugs and Vaccines 619
Adam Levy

Part VI: Injections and Implants

52. Implants and Injectables 633
Franklin W. Okumu and Jeffrey L. Cleland

53. Alzamer Depot Bioerodible Polymer Technology 639
Jeremy C. Wright, Roy Bannister, Guohua Chen, and Catherine Lucas

54. The Atrigel Drug Delivery System 647
Richard Dunn

55. Long-Term Controlled Delivery of Therapeutic Agents via an Implantable Osmotically Driven System: The DUROS Implant 657
James C. Wright, Anne E. Chester, R. Skowronski, and Catherine Lucas

56. Long-Acting Protein Formulations—ProLease Technology 671
OluFunmi L. Johnson and Paul Herbert

57. Sucrose Acetate Isobutyrate (SAIB) for Parenteral Delivery 679
Arthur J. Tipton

58. Stealth Technology 689
Frank Martin and Tony Huang

59. DepoFoam Technology 705
Sankaram Mantripragada

60. Medipad Delivery System: Controlled Macromolecule Delivery 713
Izrail Tsals and Diana Davidson

Part VII: Nasal

61. Intranasal Drug Delivery 727
Daniel P. Wermeling and Jodi L. Miller

Copyright © 2003 Marcel Dekker, Inc.

62. Poly(ethylene oxide)-*b*-Poly(propylene oxide)-*b*-Poly(ethylene oxide)-*g*-Poly(acrylic acid) Copolymers as In Situ Gelling Vehicle for Nasal Delivery 749
Lev Bromberg

Part VIII: Vaginal

63. Intravaginal Drug Delivery Technologies 759
A. David Woolfson

64. The Intravaginal Ring 775
R. Karl Malcolm

65. SupraVail Vaginal Gel 791
Mathew Leigh

66. VagiSite Bioadhesive Technology 801
R. Saul Levinson and Daniel J. Thompson

Part IX: Pulmonary

67. Pulmonary Delivery of Drugs by Inhalation 807
Igor Gonda and Jeff Schuster

68. Aerogen Pulmonary Delivery Technology 817
Paul S. Uster

69. The AERx Pulmonary Drug Delivery System 825
Jeff Schuster and S. J. Farr

70. Formulation Challenges of Powders for the Delivery of Small Molecular Weight Molecules as Aerosols 835
Anthony J. Hickey

71. Nebulizer Technologies 849
Martin Knoch and Warren Finlay

72. The Pressurized Metered-Dose Inhaler 857
Akwete L. Adjei

Copyright © 2003 Marcel Dekker, Inc.

73. Passive Dry Powder Inhalation Technology 867
Ian Ashurst and Ann Malton

74. Formulation Challenges: Protein Powders for Inhalation 879
Hak-Kim Chan

75. The Development of Large Porous Particles for Inhalation Drug Delivery 891
Richard Batycky, Daniel Deaver, Sarvajna Dwivedi, Jeffrey Hrkach, Lloyd Johnston, Tracy Olson, James E. Wright, and David Edwards

76. Dry Powder Inhalation Systems from Inhale Therapeutic Systems 903
Andy R. Clark

77. Spiros Inhaler Technology 913
Clyde Witham and Elaine Phillips

78. The Respimat, a New Soft Mist Inhaler for Delivering Drugs to the Lungs 925
Bernd Zierenberg and Joachim Eicher

79. Regulatory Issues for Pulmonary Delivery Systems 935
Darlene Rosario and Babatunde Otulana

Part X: Regulatory

80. Regulatory Issues Relating to Modified-Release Drug Formulations 943
Patrick J. Marroum

Copyright © 2003 Marcel Dekker, Inc.

Contributors

Donald E. Ackley* Redeon, Inc., Burlington, Massachusetts, U.S.A.
Akwete L. Adjei Kos Pharmaceuticals, Inc., Edison, New Jersey, U.S.A.
Syed A. Altaf, Ph.D. Gilead Sciences, Foster City, California, U.S.A.
Hemant H. Alur, Ph.D.† Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.
Gordon L. Amidon College of Pharmacy, The University of Michigan, Ann Arbor, Michigan, U.S.A.
Ian C. Ashurst, B.Sc., M.R.Pharm.S., M.Sc., Ph.D. GlaxoSmithKline, Ware, Hertfordshire, England
Anand R. Baichwal Penwest Pharm Company, Patterson, New York, U.S.A.
Roy Bannister, Ph.D., D.A.B.T. ALZA Corporation, Mountain View, California, U.S.A.
Daniel Bar-Shalom Egalet A/S, Vaerlose, Denmark
Richard Batycky Alkermes, Inc., Cambridge, Massachusetts, U.S.A.
Brian John Bellhouse, M.A., D.Phil. Department of Engineering Science, PowderJect Centre for Gene and Drug Delivery Research, University of Oxford, Oxford, England
Jörg Breitenbach, Ph.D. Abbott GmbH & Co. KG, Soliqs drug delivery business, Ludwigshafen, Germany

* *Current affiliation*: VSK Photonics, Irvine, California, U.S.A.
† *Current affiliation*: Murty Pharmaceuticals, Inc., Lexington, Kentucky, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

Lev Bromberg Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A.
Jackie Butler Elan Drug Delivery, Athlone, Ireland
Gregor Cevc, Ph.D. IDEA AG, Munich, Germany
Hak-Kim Chan, Ph.D. Faculty of Pharmacy, University of Sydney, Sydney, New South Wales, Australia
Susan A. Charman, Ph.D. Department of Pharmaceutics, Victorian College of Pharmacy, Monash University (Parkville Campus), Parkville, Victoria, Australia
William N. Charman Department of Pharmaceutics, Victorian College of Pharmacy, Monash University (Parkville Campus), Parkville, Victoria, Australia
Guohua Chen, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
Anne E. Chester, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
Sham K. Chopra Savit Consulting Inc., Brampton, Ontario, Canada
S. S. Chrai* Delsys Pharmaceutical, A Division of Elan Operations, Inc., Monmouth Junction, New Jersey, U.S.A.
Andy R. Clark Inhale Therapeutic Systems, San Carlos, California, U.S.A.
Kenneth E. Cleaver, Ph.D. Flemington Pharmaceutical Corporation, Flemington, New Jersey, U.S.A.
Jeffrey L. Cleland, Ph.D.† Genentech, Inc., South San Francisco, California, U.S.A.
Ewart T. Cole, Ph.D. Department of Research and Development, CAPSUGEL, A Division of Pfizer Inc., Arlesheim, Switzerland
Alyson L. Connor, Ph.D. Pharmaceutical Profiles Ltd, Nottingham, England
Michel Cormier, Ph.D. Biological Sciences, ALZA Corporation, Mountain View, California, U.S.A.
Rita Cortesi, Ph.D. Department of Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy
George Costigan, B.Sc., M.Phil., D.Phil. Department of Engineering Science, University of Oxford, Oxford, England
Donald P. Cox, Ph.D. Flemington Pharmaceutical Corporation, Flemington, New Jersey, U.S.A.
John R. Crison Port Systems LLC, Ann Arbor, Michigan, U.S.A.
Peter E. Daddona Biological Sciences, ALZA Corporation, Mountain View, California, U.S.A.
Diana Davidson Elan Drug Delivery, King of Prussia, Pennsylvania, U.S.A.
Daniel Deaver Alkermes, Inc., Cambridge, Massachusetts, U.S.A.
David A. Dickason Alkermes, Inc., Cincinnati, Ohio, U.S.A.

* *Current affiliation*: Chrai Associates, Cranbury, New Jersey, U.S.A.
† *Current affiliation*: Research & Development, Targesome, Inc., Palo Alto, California, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

D. Duchêne UMR, CNRS 8612 and University of Paris XI, Châtenay-Malabry, France
Harry A. Dugger III, Ph.D. Flemington Pharmaceutical Corporation, Flemington, New Jersey, U.S.A.
Richard L. Dunn, Ph.D. Atrix Laboratories, Fort Collins, Colorado, U.S.A.
Sarvajna Dwivedi, Ph.D. Alkermes, Inc., Cambridge, Massachusetts, U.S.A.
David Edwards Division of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts, U.S.A.
Joachim Eicher, Ph.D. Steag Microparts, Dortmund, Germany
Elisabetta Esposito Department of Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy
S. J. Farr Aradigm Corporation, Hayward, California, U.S.A.
Olivia Felt-Baeyens, Ph.D. School of Pharmacy, University of Geneva, Geneva, Switzerland
Warren H. Finlay, Ph.D. Department of Mechanical Engineering, University of Alberta, Edmonton, Alberta, Canada
Barrie C. Finnin Department of Pharmaceutics, Victorian College of Pharmacy, Monash University (Parkville Campus), Parkville, Victoria, Australia
T. Francis Elan Drug Delivery, Athlone, Ireland
David R. Friend, Ph.D. Delsys Pharmaceutical, A Division of Elan Operations, Inc., Monmouth Junction, New Jersey, U.S.A.
Robert M. Gale ALZA Corporation, Mountain View, California, U.S.A.
Igor Gonda Aradigm Corporation, Hayward, California, U.S.A.
George P. Grandolfi, Ph.D. Alkermes, Inc., Cincinnati, Ohio, U.S.A.
Pol-Henri Guivarc'h SkyePharma Canada Inc., Montreal, Quebec, Canada
Suneel K. Gupta, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
R. Gurny, Ph.D. School of Pharmacy, University of Geneva, Geneva, Switzerland
J. Richard Gyory* Redeon, Inc., Burlington, Massachusetts, U.S.A.
Jonathan Hadgraft, D.Sc., F.R.S.C. Medway Sciences, NRI, University of Greenwich, Chatham, England
John Hayes aForte, Chanhassen, Minnesota, U.S.A.
Paul Herbert Alkermes Incorporated, Cambridge, Massachusetts, U.S.A.
Anthony J. Hickey, Ph.D. University of North Carolina, Chapel Hill, North Carolina, U.S.A.
Jeffrey Hrkach, Ph.D. Alkermes, Inc., Cambridge, Massachusetts, U.S.A.
Tony Huang ALZA Corporation, Mountain View, California, U.S.A.
Katsumi Iga, Ph.D. Takeda Chemical Industry Ltd., Osaka, Japan

* *Current affiliation*: Transform Pharmaceuticals, Inc., Waltham, Massachusetts, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

Claudia Jacobs Department of Pharmaceutics, Biopharmaceutics and Biotechnology, Free University of Berlin, Berlin, Germany
Jette Jacobsen, M.Sc., Ph.D. Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen, Denmark
Rajni Jani, Ph.D. Department of Pharmaceutics, Alcon Research Ltd., Fort Worth, Texas, U.S.A.
OluFunmi L. Johnson, Ph.D. Alkermes Incorporated, Cambridge, Massachusetts, U.S.A.
Lloyd Johnston Alkermes Incorporated, Cambridge, Massachusetts, U.S.A.
Thomas P. Johnston, Ph.D. Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.
Oliver Kayser Department of Pharmaceutics, Biopharmaceutics and Biotechnology, Free University of Berlin, Berlin, Germany
Patrick Kearney RP Scherer, Swindon, England
Ian W. Kellaway, D.Sc., F.R.Pharm.S. School of Pharmacy, University of London, London, England
Mark A. F. Kendall, B.G., Ph.D. Department of Engineering Science, PowderJect Centre for Gene and Drug Delivery Research, University of Oxford, Oxford, England
Janez Kerč, Ph.D. Research and Development Division, Lek Pharmaceutical and Chemical Company, Ljubljana, Slovenia
Rajendra K. Khankari, Ph.D. CIMA LABS INC, Brooklyn Park, Minnesota, U.S.A.
Martin Knoch, Ph.D. PARI GmbH, Starnberg, Germany
Joseph Kost, Ph.D. Department of Chemical Engineering, Sontra Medical, Cambridge, Massachusetts, U.S.A.
Markus Krumme, Ph.D. LTS Lohmann Therapie-Systeme AG, Andernach, Germany
Gary B. Kupperblatt, Ph.D.* Delsys Pharmaceutical, A Division of Elan Operations, Inc., Monmouth Junction, New Jersey, U.S.A.
Jaehwi Lee, Ph.D. School of Pharmacy, Purdue University, West Lafayette, Indiana, U.S.A.
Wang Wang Lee Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland
Mathew Leigh, B.Pharm., M.R.Pharms., Ph.D. Phares Drug Delivery AG, Muttenz, Switzerland
R. Saul Levinson, Ph.D. KV Pharmaceutical Company, St. Louis, Missouri, U.S.A.

* *Current affiliation*: Department of Chemical Sciences, The Dow Chemical Company, Midland, Michigan, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

Adam Levy, B.A., M.A., M.B.A. Weston Medical Group plc, Trumpington, England
Jon Lewis, B.Sc., Ph.D. Abbott GmbH & Co. KG, Soliqs drug delivery business, Ludwigshafen, Germany
Catherine Lucas, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
R. Karl Malcolm, Ph.D. Pharmaceutical Formulation Research Unit, School of Pharmacy, Queen's University Belfast, Belfast, Northern Ireland
Ann Malton Inhalation Product Development, GlaxoSmithKline R&D, Ware, Hertfordshire, England
Sankaram Mantripragada, Ph.D. SkyePharma Inc., San Diego, California, U.S.A.
Patrick J. Marroum, Ph.D. Division of Pharmaceutical Evaluation I, Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, U.S.A.
Frank Martin ALZA Corporation, Mountain View, California, U.S.A.
Troy W. McCall Penwest Pharm Company, Patterson, New York, U.S.A.
B. McKenna Elan Drug Delivery, Athlone, Ireland
E. Menegatti Department of Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy
Jodi L. Miller, Pharm.D., M.S. College of Pharmacy, University of Kentucky, Lexington, Kentucky, U.S.A.
Awadhesh K. Mishra, Ph.D. SkyePharma Canada Inc., Montreal, Quebec, Canada
Ashim K. Mitra, B.S., M.S., Ph.D. Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.
Samir Mitragotri, Ph.D. Department of Chemical Engineering, University of California, Santa Barbara, California, U.S.A.
Derek V. Moe, Ph.D. CIMA LABS Inc., Brooklyn Park, Minnesota, U.S.A.
Donald C. Monkhouse, Ph.D. Therics, Inc., Princeton, New Jersey, U.S.A.
Timothy M. Morgan, Ph.D., P.M.P. Acrux Limited, Melbourne, Victoria, Australia
Gour Mukherji, Ph.D. Ranbaxy Laboratories Ltd., Gurgaon, India
Rainer Helmut Müller, Ph.D. Department of Pharmaceutics, Biopharmaceutics and Biotechnology, Free University of Berlin, Berlin, Germany
Ramaswamy Murari, Ph.D. Delsys Pharmaceutical, A Division of Elan Operations, Inc., Monmouth Junction, New Jersey, U.S.A.
Claudio Nastruzzi, Ph.D. Department of Chemistry and Pharmaceutical Technology, University of Perugia, Perugia, Italy
Franklin W. Okumu Genentech, Inc., South San Francisco, California, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

Tracy Olson Alkermes, Inc., Cambridge, Massachusetts, U.S.A.
Babatunde Otulana, M.D. Aradigm Corporation, Hayward, California, U.S.A.
Gary W. Pace* SkyePharma Canada Inc., Montreal, Quebec, Canada
Rama V. Padmanabhan, Ph.D. ALZA Corporation, Mountain View, California. U.S.A.
Rodney M. Panos, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
Franklin Pass Antares Pharma, Inc., Minneapolis, Minnesota, U.S.A.
S. Indiran Pather, D.Pharm. CIMA LABS INC., Brooklyn Park, Minnesota, U.S.A.
Elaine Phillips Elan Pharmaceutical Technologies, San Diego, California, U.S.A.
J. Bradley Phipps, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
Bernard Plazonnet, Ph.D. Laboratory of Sensory Biophysics, University of Auvergne, Clermont-Ferrand, France
Gilles Ponchel UMR, CNRS 8612 and University of Paris XI, Châtenay-Malabry, France
Mark R. Prausnitz, Ph.D. School of Chemical Engineering, Georgia Institute of Technology, Atlanta, Georgia, U.S.A.
David V. Prior, Ph.D., M.R.S.C., C.Chem. Pharmaceutical Profiles Ltd, Nottingham, England
L. Sesha Rao, Ph.D. Chauvin Pharmaceuticals Ltd., Romford, Essex, England
Araz A. Raoof, Ph.D. Elan Drug Delivery, Athlone, Ireland
Margrethe Rømer Rassing, M.Sc., Ph.D. Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen, Denmark
Barry L. Reed Department of Pharmaceutics, Victorian College of Pharmacy, Monash University (Parkville Campus), Parkville, Victoria, Australia
Erin Rhone Pharmaceutical Research and Development, Alcon Research Ltd., Fort Worth, Texas, U.S.A.
Darlene Rosario Aradigm Corporation, Hayward, California, U.S.A.
Charles W. Rowe Therics, Inc., Princeton, New Jersey, U.S.A.
Jeff Schuster, Ph.D. Aradigm Corporation, Hayward, California, U.S.A.
John M. Siebert, Ph.D. CIMA LABS INC., Brooklyn Park, Minnesota, U.S.A.
Roman J. Skowronski, M.D., Ph.D.† ALZA Corporation, Mountain View, California, U.S.A.
Lillian Slot Department of New Drug Development, Egalet A/S, Vaerlose, Denmark
Robert A. Snow, Ph.D., M.B.A. SkyePharma Canada Inc., Montreal, Quebec, Canada

* *Current affiliation*: QRx Pharma Inc., Winchester, Massachusetts, U.S.A.
† *Current affiliation*: Alexza Molecular Delivery Corporation, Palo Alto, California, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

Wilfred Aubrey Soskolne, B.D.S., Ph.D. The Department of Periodontology, Hebrew University–Hadassah Faculty of Dentistry, Jerusalem, Israel
John N. Staniforth Vectura Ltd, University of Bath Campus, Bath, England
Howard N. E. Stevens Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, Scotland
Barbara E. Stewart, Ph.D. Nonclinical Research and Development, ALZA Corporation, Mountain View, California, U.S.A.
Daniel J. Thompson, M.S., J.D. Department of Scientific Affairs, KV Pharmaceutical, St. Louis, Missouri, U.S.A.
Arthur J. Tipton Southern BioSystems, Birmingham, Alabama, U.S.A.
Izrail Tsals Elan Drug Delivery, King of Prussia, Pennsylvania, U.S.A.
Paul S. Uster Aerogen Inc., Mountain View, California, U.S.A.
Michael G. Vachon, M.Sc.Phm., Ph.D. SkyePharma Canada Inc., Montreal, Quebec, Canada
William W. van Osdol, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
John L. Vieira Port Systems LLC, Ann Arbor, Michigan, U.S.A.
Michael Walker ConvaTec Wound Care and Prevention Global Development Centre, Deeside, Flintshire, England
Chen-Chao Wang, Ph.D. Department of Research and Development, Therics, Inc., Princeton, New Jersey, U.S.A.
Daniel P. Wermeling, Pharm.D. College of Pharmacy, University of Kentucky, Lexington, Kentucky, U.S.A.
Ian R. Wilding, Ph.D. Pharmaceutical Profiles, Nottingham, England
Clive G. Wilson, Ph.D. Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland
Sylvia Andrea Wissing, Ph.D. Department of Pharmaceutics, Biopharmaceutics and Biotechnology, Free University of Berlin, Berlin, Germany
Clyde Witham Elan Pharmaceutical Technologies, San Diego, California, U.S.A.
Patrick S. L. Wong, Ph.D. ALZA Corporation, Mountain View, California, U.S.A.
A. David Woolfson, Ph.D. School of Pharmacy, Queen's University Belfast, Belfast, Northern Ireland
James E. Wright Alkermes, Inc., Cambridge, Massachusetts, U.S.A.
Jeremy C. Wright, Ph.D.* ALZA Corporation, Mountain View, California, U.S.A.
Wendy Young ALZA Corporation, Mountain View, California, U.S.A.
Horst G. Zerbe, Ph.D. Smartrix Technologies Inc, Kirkland, Quebec, Canada
Bernd Zierenberg, Ph.D. Boehringer Ingelheim Pharma KG, Ingelheim, Germany

* *Current affiliation*: DURECT Corporation, Cupertino, California, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

1

Oral Modified-Release Delivery Systems

Susan A. Charman and William N. Charman
Victorian College of Pharmacy, Monash University (Parkville Campus), Parkville, Victoria, Australia

I. INTRODUCTION

The oral route of drug delivery is typically considered the preferred and most patient-convenient means of drug administration. Consequently, much effort is directed during drug discovery to identify orally active candidates that will provide reproducible and effective plasma concentrations in vivo. The reality is that many compounds are either incompletely or ineffectively absorbed after oral administration (i.e., bioavailability is an issue), or that the required dosing frequency is too short to enable once- or twice-daily administration (i.e., pharmacokinetic half-life is an issue). Lead optimization typically addresses such shortcomings during a discovery program; however, in many cases it is not possible to identify an appropriate clinical candidate with the requisite "ideal" physicochemical and/or pharmacokinetic properties. For clinical research phase drug candidates, or drugs already marketed, the opportunity for enhancing their clinical pharmacology profile after oral administration through attainment of more optimal blood drug concentration-time profiles should always be considered.

Modified-release formulation technologies offer an effective means to optimize the bioavailability and resulting blood concentration-time profiles of drugs that otherwise suffer from such limitations. Within the context of this chapter, the term "modified release" refers to both delayed- and extended-release systems for oral administration as well as oral delivery systems designed specifically to modify the release of poorly water-soluble drugs. Also included are the fast-dissolving dosage forms for which absorption occurs primarily (but not exclu-

Copyright © 2003 Marcel Dekker, Inc.

sively) in the gastrointestinal (GI) tract. The chapters in this part describe a broad range of pharmaceutical formulation technologies that address various limiting features associated with oral drug bioavailability and dosing frequency. In planning this part, we invited technology-focused chapters from expert contributors who had direct experience with the individual systems. Our goal was to select relatively advanced technologies representative of the various contemporary approaches being taken in the field—our success in this endeavor is a direct consequence of the willingness of the contributing authors who graciously accepted our invitation. As with all written compilations of this nature, time, commercial, and intellectual property restrictions on the part of potential contributors unfortunately precluded the description of some highly relevant and successful technologies.

II. PHYSIOLOGICAL AND PHYSICOCHEMICAL CONSIDERATIONS IN THE DESIGN OF ORAL MODIFIED-RELEASE FORMULATIONS

The human GI tract is a complex time-, position-, and patient-dependent absorptive, metabolizing, and excretive organ. Key physiological factors that control the absorption of drugs from the GI tract include gastric and intestinal transit profiles, fluid and food intake, bulk fluid and luminal pH, gastric and intestinal secretions, absorptive mechanisms, and enterocyte-based metabolism and secretion (efflux). Coupled with these physiological factors, the physicochemical properties of a drug, such as its solubility, ionization, stability, and lipophilicity, strongly influence the rate and extent of drug absorption from the GI lumen. A critical assessment of fundamental physicochemical properties and a consideration of their interplay with the physiological constraints of the GI tract are paramount to the successful design of modified-release oral drug delivery systems. Ideally, oral extended-release systems rely upon the dosage form to control the rate of drug release with little or no effect from the intrinsic properties of the drug or the conditions prevailing within the GI tract. Realistic candidates exhibit high permeability across the GI epithelium (Class I and Class II drugs according to the Biopharmaceutic Classification System [1]) such that their absorption rate is controlled exclusively by the rate of release from the dosage form. It is only under these conditions that in vitro dissolution rates can possibly be used to predict in vivo absorption rates and guide formulation development.

Perhaps the greatest challenge in the design of oral modified-release formulations and the establishment of useful in vitro–in vivo correlations is the changing nature of the GI tract from the stomach to the colon [2]. While the vast majority of drugs delivered in immediate-release preparations are absorbed from the upper regions of the small intestine, extended-release preparations rely upon

Copyright © 2003 Marcel Dekker, Inc.

absorption throughout the small intestine and sometimes into the colon. A recent report of the regional absorption of late phase I new chemical entities indicated that for the majority of compounds tested, absorption decreased significantly in the distal intestine [3]. Site-dependent permeability greatly complicates the establishment of useful in vitro–in vivo correlations and potentially leads to variable absorption due to transit time variations both within and between patients. Furthermore, the recent identification of efflux-dependent drug permeability, with the associated linkage to enterocyte-based metabolism mediated via cytochrome P450, further complicates the predictability of drug absorption and bioavailability for modified-release dosage forms. This results from the dependence of efflux/metabolism interactions on local drug concentrations, which are typically lower from a modified-release product than an immediate-release product. Regional drug exposure (greater distal intestinal exposure with modified release compared with an immediate-release product) also contributes to variations in efflux and metabolism as expression and activity of both Pgp [4] and CYP3A4 [5] vary along the length of the GI tract.

Transit time through the GI tract is a major factor that impacts the effectiveness of modified-release dosage forms as it directly influences the site of drug release. Differing sites of drug release, as a function of transit profiles, require assessment of the changing pH and water content on subsequent drug absorption

Table 1 Approximate Fluid Flux, pH, and Residence Times Within the Gastrointestinal Tract

Section	Fluid	Input/day (mL)		Output/day (mL)	pH[a]	Residence time (h)
Mouth	Water + saliva	1200 + 1500				
Stomach	Gastric fluid	2000[a]			1–3.5	0.5–12[a,b]
	Pancreatic juice	1500				
Duodenum					4–6.5	
	Bile	500				3–4[c]
Jejunum					5–7	
	Intestinal secretions	1500	→	8500		
Ileum					6–8	
Colon	Fluid transfer	500	→	350	6–8	~10[d]

Source: Adapted from Refs. 6,7,25,27.

[a] Varies depending on the postprandial state.

[b] Highly dependent on dosage form size.

[c] Relatively independent of dosage form size and postprandial state.

[d] Not well defined.

Copyright © 2003 Marcel Dekker, Inc.

(Table 1) [6,7]. While the rate of gastric emptying varies markedly depending on the state (i.e., solid or liquid) and size of the dosage forms (i.e., multiparticulate or monolithic) and on the presence and composition of food [8], intestinal transit times for liquids or solids, in either the fed or fasted state, are relatively constant at approximately 3–4 h [9]. Hence, for a compound with limited permeability in the large intestine, this narrow window for intestinal release may limit the potential utility of an extended-release dosage form. The interplay between GI physiology (e.g., transit, environment) and formulation design (e.g., type of formulation, mechanism of release) is always a key determinant of the likely success of modified-release drug products.

III. RECENT ADVANCES AND FUTURE DIRECTIONS IN MODIFIED-RELEASE DELIVERY SYSTEMS FOR ORAL ADMINISTRATION

While significant advances have been made in the development of elegant systems to modify the oral delivery of drugs, the basic approaches have remained largely unchanged with the major systems being (a) insoluble, slowly eroding, or swelling matrices, (b) polymer-coated tablets, pellets, or granules, (c) osmotically driven systems, (d) systems controlled by ion exchange mechanisms, and (e) various combinations of these approaches. The scientific literature is full of other intricate and complex examples of oral modified-release systems, but the commercial applicability and success of many of these systems/devices has yet to be realized.

Over the past 20 years, advances in oral modified-release technologies have been largely driven by significant improvements in manufacturing equipment, most notably coating equipment, as well as the development of improved biocompatible and biodegradable polymeric materials for controlling release rates [10]. A further driving force has been the development of a greater appreciation by both pharmaceutical scientists and regulatory authorities of the impact of physiological variability on the performance of modified-release products leading to more stringent requirements to ensure their safety and efficacy. Establishing in vitro–in vivo (Fig. 1) for modified-release systems has become almost mandatory for establishing dosage form design criteria and for setting appropriate in vitro dissolution limits and specifications to ensure acceptable in vivo performance [2,11].

Monolithic matrices continue to be extensively utilized for the preparation of oral modified-release delivery systems owing to their simplicity and ease of manufacture using conventional processing equipment. Matrix systems generally consist of dissolved or dispersed drug within a swelling or slowly eroding polymer matrix. Drug release from these systems is governed by water penetration into the matrix followed by the diffusion of drug into the surrounding medium,

Copyright © 2003 Marcel Dekker, Inc.

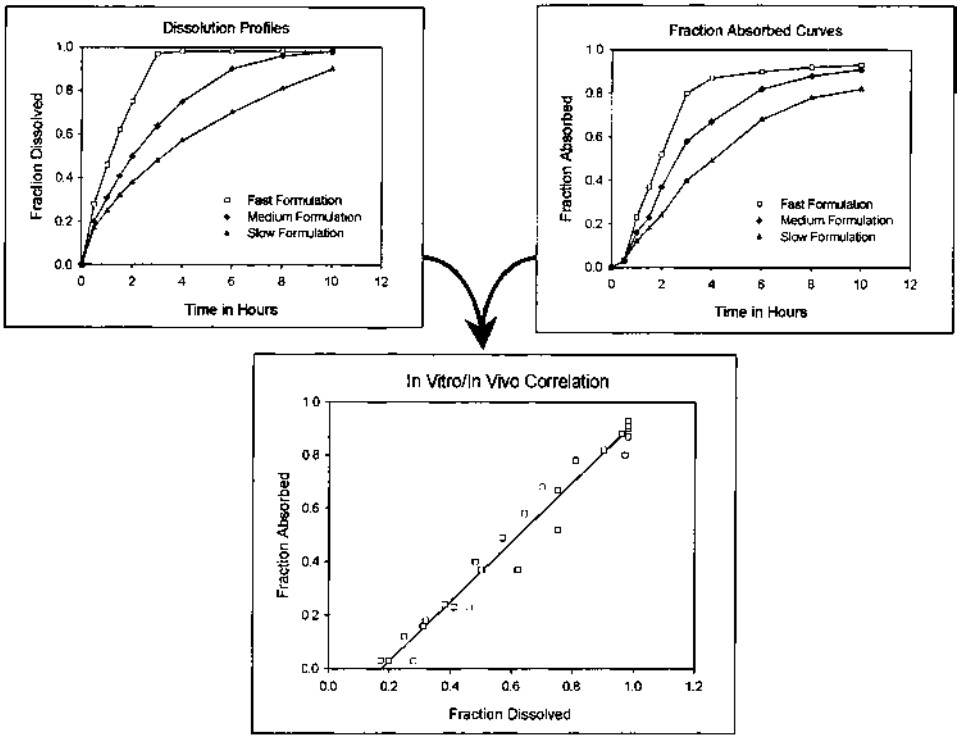


Figure 1 Development of an in vivo/in vitro correlation. (Adapted from Ref. 11.)

erosion of the matrix, or combination of the two. Hydrophilic gums, which form a viscous release-retarding gel layer upon hydration, continue to show popularity for use in oral modified-release systems. The TIMERx® technology (Chapter 2) incorporates a combination of xanthan gum and locust bean gum together with a saccharide component to form a rate-controlling matrix system. The MASRx™/COSRx technologies (Chapter 3) utilize guar gum as the rate-controlling polymer and resulting tablets can be further film-coated to obtain the desired release profile. Another such system, Contramid® [12], incorporates a biodegradable, cross-linked high amylose starch as the rate-controlling tablet matrix.

A potential disadvantage of the simple monolithic matrix systems is the lack of zero-order release kinetics resulting from time-dependent changes in the diffusional path length and surface area. Several systems have been designed to overcome this limitation by modifying the matrix geometry such that the surface area available for diffusion increases with time to compensate for the increase in the diffusional distance. One such tablet system (Procise™, Chapter 4) incorpo-

Copyright © 2003 Marcel Dekker, Inc.

rates a coated geometric core in which diffusion occurs only from the cylindrical face of the disc. A banded capsule-shaped matrix tablet (RingCap™, Chapter 5) has also been described and is based on similar geometric principles for controlling the diffusion rate. Yet another variation to the geometric approach is the complex multilayered tablet, such as Smartrix® (Chapter 6) in which a geometrically designed core is combined with slowly eroding cover layers to control the release of active drug. The Geometrix® technology represents a further system that operates on the same principle by combining a matrix core with modulating layers in a multilayer tablet configuration to provide linear, pulsatile, and delayed release of drugs [13].

In recent years, there has been an increase in the application of related technologies to the fabrication of modified-release dosage forms for drugs. One such system, TheriForm™ (Chapter 7) is based on Three Dimensional Printing™ technology and uses a layer-by layer approach to accurately control the internal microstructure of the dosage form to provide complex release profiles. Another example, Accudep™ technology (Chapter 8) uses electrostatic deposition, similar to that used in copy machines for the precise deposition of ink particles, in combination with erosional polymeric film barriers to achieve sustained or pulsatile release profiles of active materials. The LeQtracoat™ and LeQtradose™ technologies also utilize dry powder electrostatic deposition to enable tablet coating and/or precise drug loading [14].

Osmotically controlled oral delivery systems (Oros®, Chapter 9) were initially described in the 1970s and have since been applied to a number of different drug products. The basic operation of these systems relies upon the osmotically driven influx of water through a semipermeable membrane followed by displacement of drug and release through an orifice. The elementary osmotic pump, along with more specialized variations to the basic configuration, enable the controlled delivery of actives with varying aqueous solubilities.

Multiparticulate dosage forms offer a number of potential advantages over monolithic preparations in terms of their dispersion characteristics, transit times through the GI tract, and reduced potential for gastric irritation. Classical extrusion, spheronization, and pellitization processes typically result in pellets with irregular surfaces and out of varying sizes, which are inherently more difficult to film-coat. A recent report described the preparation of almost perfectly spherical particles with a narrow size distribution for improved coating efficiency (Ceform™, [15]). A number of patented technologies for multiparticulate dosage forms have recently been described, such as the Micropump® system [16], which is an osmotically driven coated microparticle system designed to increase the absorption time for rapidly absorbed drugs. Polymer coating materials and processing technologies have advanced significantly in recent years and future development of new and improved polymers will be guided by regulatory and environmental pressure to reduce or eliminate organic solvents from coating processes [10].

Copyright © 2003 Marcel Dekker, Inc.

The increased emergence of poorly water-soluble active compounds presents specific obstacles for the development of both immediate-release and modified-release dosage forms. Poorly water-soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution and solubilization of these agents are typically more affected by the postprandial state, gastric, pancreatic, and biliary secretions, and pH [17]. The challenge for poorly soluble drugs is to control the rate of dissolution to minimize variations and maintain a well-dispersed system that allows the drug to be absorbed. Chemical approaches to facilitate this aim, such as incorporation of Cyclodextrin derivatives as solubilizing agents into modified-release systems [18], may also show increased utility in future applications.

One approach to overcome the dissolution limitation of poorly water-soluble drugs is the formulation of active drug in an amorphouse form, which overcomes many of the potential problems associated with changes in particle size, crystallinity, and polymorphism. In the Threeform system (Chapter 10), amorphous drug is first stabilized by a mixture of surfactant and polymers and is then incorporated into a polymeric matrix that is finally coated with a rate-controlling film. In a different approach, the Meltrex™ technology (Chapter 11) uses a solvent-free, melt extrusion method to form a solid dispersion of amorphous material that releases drug through diffusion and erosion.

A parallel strategy for the delivery of drugs with poor aqueous solubility is a reduction in particle size through the preparation of nanoparticles or microparticles. High-pressure homogenization is utilized to form a nanosuspension in the DissoCube® technology (Chapter 12), which facilitates drug dissolution and increases the saturation solubility. The resulting nanosuspension can then be combined with traditional dosage forms to produce tablets or capsules with improved dissolution of active drug. The NanoCrystal® technology incorporates a proprietary milling technique whereby agglomeration of the resulting particles is prevented by surface adsorption of GRAS stabilizers [19]. The IDD™ technology (Chapter 13) produces drug microparticles that are stabilized by surface-modifying agents, such as phospholipids, to provide a capsule domain that inhibits particle growth due to aggregation, flocculation, agglomeration, or Ostwald ripening. The resulting suspension can then be dried by lyophilization, spray drying, or other suitable drying technique and incorporated into a convenient dosage form.

The introduction of liquid-filled and sealed hard gelatin capsules (Chapter 14) has provided new opportunities for the development of liquid and semisolid dosage forms for poorly water-soluble drugs. This capsule technology can incorporate liquid and semisolid lipophilic vehicles and various solubilizing agents to improve the dissolution and dispersion properties in an attempt to obtain maximal and reproducible bioavailability.

It has been increasingly recognized that compliance issues with solid oral dosage forms can be significant for those individuals who have difficulty in swal-

Copyright © 2003 Marcel Dekker, Inc.

lowing, particularly pediatric and geriatric patients. Fast-dissolving dosage forms have recently been developed as a convenient means of overcoming this problem while maintaining the processing and stability advantages of solid dosage forms. The Zydis® technology (Chapter 15), one of the first such technologies to be introduced in the market, utilizes lyophilization to produce a "fast-melting" dosage form that can be taken without water. Other variations include the OraSolv® system (Chapter 16) which relies on the presence of water-soluble excipients and use of low-compression forces to produce a highly porous tablet that disintegrates rapidly, and the related DuraSolv™ technology (Chapter 16), which incorporates soluble, fine-particle fillers to enhance dissolution while producing a more robust compressed tablet preparation.

Future directions in oral modified-release technology will be largely guided by the changing properties of active pharmaceutical compounds. As emerging molecules trend toward increasing hydrophobicity and/or lipophilicity, the need and requirement for dosage forms to facilitate the release of these poorly soluble compounds is likely to increase. Dosage forms that enhance the solubility and dissolution rate, such as the amorphous, nanoparticulate, and microparticulate systems, and those that incorporate solubilizing excipients such as modified cyclodextrins [20], are likely to be increasingly employed. With the availability of new encapsulation technologies for liquid dosage forms, self-emulsifying lipid/surfactant systems [21] may also show greater utilization for poorly soluble drugs. Poorly permeable, high-molecular-weight compounds (e.g., peptides and proteins) present further, and significant, challenges for oral delivery and numerous groups are actively researching delivery strategies for this class of drugs. Current and future approaches include various particulate systems [22], natural polymeric penetration enhancers such as chitosans [23], and prodrug approaches [24].

A further key driver for the development and commercialization of modified-release technologies will be the realization that the pharmacodynamic profile of a drug might be enhanced by administering it in a modified-release oral dose form compared with a conventional immediate-release product. Although the history of modified-release does form has been largely technology focused, the future may well build on this technology base to embrace and explore opportunities to enhance the pharmacodynamic profile of candidate drugs.

REFERENCES

1. GL Amidon, H Lennernas, VP Shah, JR Crison. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 12:413–420, 1995.
2. E Lipka, GL Amidon. Setting bioequivalence requirements for drug development based on preclinical data: optimizing oral drug delivery systems. J Control Rel 62: 41–49, 1999.

Copyright © 2003 Marcel Dekker, Inc.

3. D Gardner, R Casper, F Leith, IR Wilding. The InteliSite capsule: a new easy to use approach for assessing regional drug absorption from the gastrointestinal tract. Pharm Technol Eur 9:46–53, 1997.
4. G Fricker, J Drewe, J Huwyler, H Gutmann, C Beglinger. Relevance of p-glycoprotein for the enteral absorption of cyclosporin A: in vitro–in vivo correlation. Br J Pharmacol 118:1841–1846, 1996.
5. MF Paine, M Khalighi, JM Fisher, DD Shen, KL Kunze, CL Marsh, JD Perkins, KE Thummel. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmacol Exp Ther 283:1552–1562, 1997.
6. JB Dressman, GL Amidon, C Reppas, VP Shah. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm Res 15:11–22, 1998.
7. R Lobenberg, GL Amidon. Modern bioavailability, bioequivalence and biopharmaceutics classification system: new scientific approaches to international regulatory standards. Eur J Pharm Biopharm 50:3–12, 2000.
8. IR Wilding, AJ Coupe, SS Davis. The role of γ-scintigraphy in oral drug delivery. Adv Drug Del Rev 46:103–124, 2001.
9. SS Davis, FN Christensen, JG Hardy. The intestinal transit of pharmaceutical dosage forms. Gut 27:886–892, 1986.
10. CT Rhodes, SC Porter. Coatings for controlled-release drug delivery systems. Drug Dev Ind Pharm 24:1139–1154, 1998.
11. VRS Uppoor. Regulatory perspectives on in vitro (dissolution)/in vivo (bioavailability) correlations. J Control Rel 72:127–132, 2001.
12. V Lenaerts, I Moussa, Y Dumoulin, F Mebsout, F Chouinard, P Szabo, MA Mateescu, L Cartilier, R Marchessault. Cross-linked high amylose starch for controlled release of drugs: recent advances, J Control Rel 53:225–234, 1998.
13. U Conte, L Maggi. A flexible technology for the linear, pulsatile and delayed release of drugs, allowing for easy accommodation of difficult in vitro targets. J Control Rel 64:263–268, 2000.
14. HE Hogan, JN Staniforth, L Reeves, T Page. Electrostatic coating. US Patent 6,117,479, 1997.
15. JC Richards, DV Prior, SE Frisbee, J Getz, IR Wilding. Pharmacoscintigraphic evaluation of novel controlled release microsphere (Ceform) formulations. Proc Int Symp Control Rel Bioact Mater 25:920–921, 1998.
16. C Castan, M Cicquel, R Meyrueix, P Autant, R Jorda, P Vivet, G Soula. Genvir: the first sustained release dosage form of acyclovir. Proc Int Symp Control Rel Bioact Mater 27:1198–1199, 2000.
17. WN Charman, CJH Porter, S Mithani, JB Dressman. Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharm Sci 86:269–282, 1997.
18. MR Venkatramana, JL Haslam, VJ Stella. Controlled release matrices of poorly water soluble drugs using $(SBE)_{7M}$-β-CD as a solubilizing agent. Proc Int Symp Control Rel Bioact Mater 26:929–930, 1999.
19. GG Liversidge, KC Cundy, JF Bishop, DA Czekai. Surface modified drug nanoparticles. US Patent 5,145,684, 1992.
20. RA Rajewski, VJ Stella. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. J Pharm Sci 85:1142–1169, 1996.

Copyright © 2003 Marcel Dekker, Inc.

21. CW Pouton. Formulation of self-emulsifying drug delivery systems. Adv Drug Del Rev 25:47–58, 1997.
22. R Langer, H Chen. Oral particulate delivery: status and future trends. Adv Drug Del Rev 34:339–350, 1998.
23. L Illum. Chitosan and its use as a pharmaceutical excipient. Pharm Res 15:1326–1331, 1998.
24. GM Pauletti, S Gangwar, TJ Siahaan, J Aube, RT Borchardt. Improvement of oral peptide bioavailability: peptidomimetics and prodrug strategies. Adv Drug Del Rev 27:235–256, 1997.
25. KH Bauer, K Lehmann, HP Osterwald, G Rothgang. Coated Pharmaceutical Dosage Forms. Boca Raton, FL: CRC Press LLC, 1998, pp 126–130.
26. IR Wilding. Evolution of the biopharmaceutics classification system (BCS) to oral modified release (MR) formulations; what do we need to consider? Eur J Pharm Sci 8:157–159, 1999.

Copyright © 2003 Marcel Dekker, Inc.

2

TIMERx Oral Controlled-Release Drug Delivery System

Troy W. McCall and Anand R. Baichwal
Penwest, New York, New York

John N. Staniforth
Vectura Ltd., Bath, England

I. INTRODUCTION

The novel oral controlled-release drug delivery system TIMERx® is a pregranulated blend composed of synergistic heterodisperse polysaccharides (usually xanthan gum and locust bean gum) together with a saccharide component (generally dextrose) [1]. The technology is capable of delivery a wide range of drugs and is customized to accommodate a variety of physicochemical and pharmacokinetic properties and release profiles. The material has uniform packing characteristics over a range of different particle size distributions and is capable of processing into tablets using either direct compression, following addition of drug and lubricant, or conventional wet granulation. The synergism between the homo- and heteropolysaccharide components of the system enables formulation manipulation of different rate-controlling mechanisms. The ultimate rate of drug release is controlled by the rate of water penetration into the matrix. The technology is well protected with over 90 patents issued worldwide [2–4].

Drug release from tablets containing the polysaccharide system is capable of control using a variety of different formulations and process methods to provide a variety of release modalities that are capable of matrix-dimension independence. Control of drug release is achieved by manipulation of the synergistic interactions of the heterodisperse polysaccharides to regulate the rate of water

Copyright © 2003 Marcel Dekker, Inc.

penetration into the tablet and subsequent diffusion of the drug across the gel layer.

II. HISTORICAL DEVELOPMENT

The TIMERx technology was conceived based on the premise that oral controlled-release systems do not have to be complicated to possess superior in vitro and in vivo performance characteristics. At the time the technology was invented, the predominant systems available were: (a) hydrophilic matrices, (b) oral osmotic pumps, and (c) multiparticulates (beads). Clearly, conventional matrix tablets represented the most simple, but possessed a number of weaknesses including polymer variablity, difficulty in achieving zero-order release, little or no ability to maintain a strong proprietary position, and problems in consistently releasing drug for extended periods (i.e., 12–24 h). On the other hand, oral osmotic and multiparticulate systems overcame these problems but were difficult to develop and manufacture on standard solid-dosage-form processing equipment. In their simplest forms, TIMERx tablet formulations consist of drug, bulk TIMERx, and lubricant, and are processed using conventional tableting equipment. This is in contrast to other matrix systems that require evaluation of numerous polymers to optimize drug release and typically need flow and compressibility aids to permit tablet production. Therefore, the TIMERx technology was developed to retain the simplicity of conventional matrix systems while overcoming the problems associated with the more complicated technologies.

III. DESCRIPTION OF THE TECHNOLOGY

A. Physical Characteristics of the Ungelled (Unwetted) System

Particle size distributions of some controlled release formulations developed for different drugs show that the modal diameters vary from approximately 195 μm to 215 μm. In some cases, the size distributions are unimodal, while in others, some bimodality is evident. Other differences include the degree of kurtosis and skewness of the distributions. These factors may be important in optimizing the mechanical properties, content uniformity, and release-sustaining characteristics of a direct compression formulation for a given drug. Alternatively, in the case of a wet granulation system, the particle size distribution, as well as the agglomerating properties, may be important. Notwithstanding the different particle size distributions available, it is interesting to note that the packing behavior results in loose and consolidated bulk densities (and Hausner ratios), which remain virtually constant. This is a potentially valuable property in view of the dependency of

Copyright © 2003 Marcel Dekker, Inc.

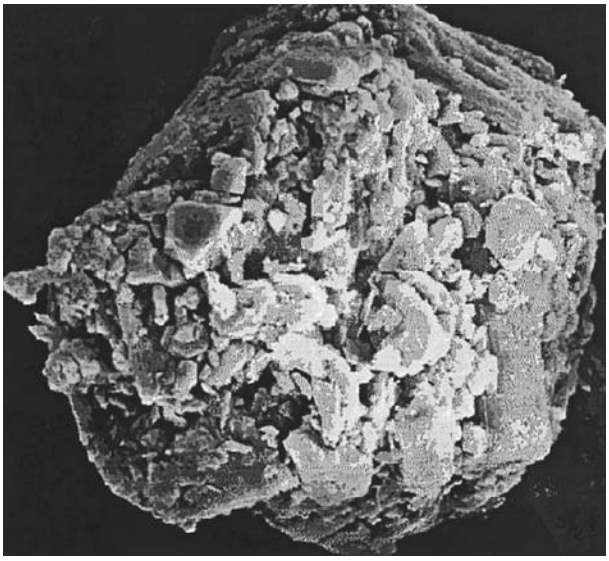


Figure 1 Scanning electron micrograph of a single heterodisperse polysaccharide agglomerate in the unwetted state.

powder flow and hence tablet weight and content uniformity on powder packing characteristics.

The surface morphology of the particles of the TIMERx system provides a generally regular, near-spherical particle shape, which helps to confer good flow properties (Fig. 1). The surface texture is relatively rough with clefts and large pores capable of conferring segregation resistance on the direct compression formulation.

Tablets compacted using an instrumented rotary tablet machine possess strength profiles that are largely independent of the saccharide component. Scanning electron photomicrographs of ungelled tablet surfaces provide qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface. There is also evidence of surface pores through which initial solvent ingress and solution egress may occur.

B. Physical Characteristcs of the Gelled (Wetted) System

The properties and characteristics of the specific heterodisperse polysaccharide system are dependent on the individual characteristics of polysaccharide constituents, in terms of polymer solubility, glass transition temperatures, etc., as

Copyright © 2003 Marcel Dekker, Inc.

well as on the synergism both between different polysaccharides and between polysaccharides and saccharides in modifying dissolutions fluid-excipient interactions.

For example, the heteropolysaccharide xanthan gum has a molecular weight of approximately 300,000–1,000,000, and is readily soluble, which as a homodisperse system produces a highly ordered, helical or double-helical molecular conformation that provides high viscosity without gel formation. In contrast, a homodisperse system of the homopolysaccharide, locust bean gum, is only slowly soluble and ungelled at low temperatures. Prolonged exposure to the dissolution fluid promotes solubilization, which allows molecules to associate and undergo gelation as the result of intermacromolecular cross-linking in ribbon or helical "smooth" regions. The heterodisperse system contains both hetero- and homopolysaccharides, which exhibit synergism. The heteropolysaccharide component acts to produce a faster gelation of the homopolysaccharide component and the homopolysaccharide acts to cross-link the normally free heteropolysaccharide helices (Fig. 2). The resultant gel is faster forming and more rigid. The viscosity and solubilization speed are further potentiated by the saccharide component. Gel rigidity may also be further potentiated in the presence of some cations and anions. A diagram of the interactions occurring between the different materials is provided in Figure 3.

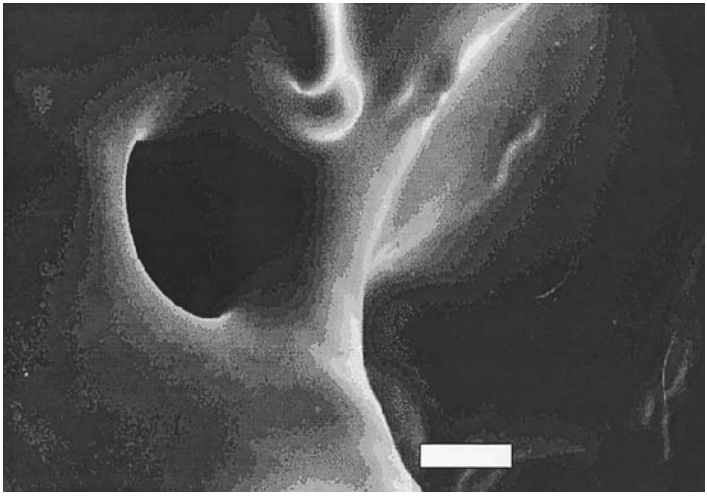


Figure 2 Scanning electron micrograph of the gelled (wetted) heterodisperse polysaccharide tablet showing pore formation.

Copyright © 2003 Marcel Dekker, Inc.

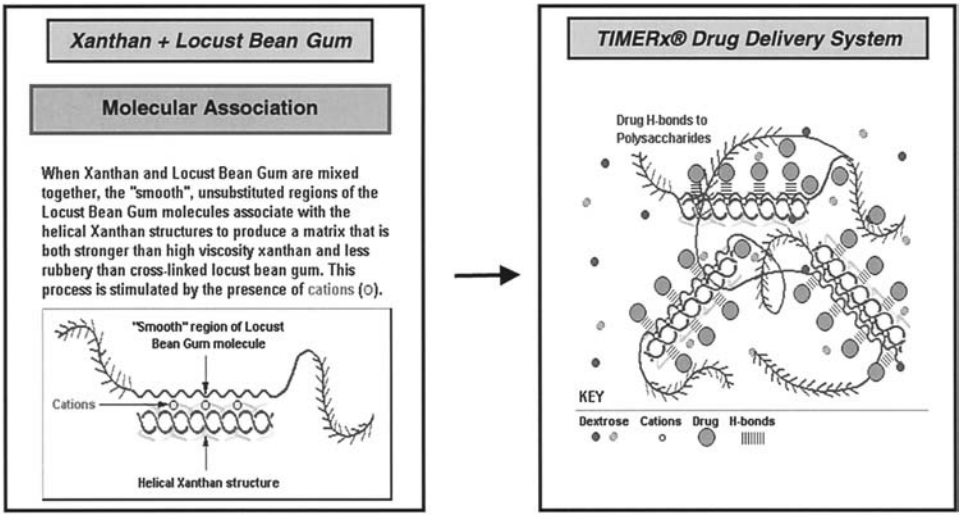

Xanthan + Locust Bean Gum
Molecular Association
When Xanthan and Locust Bean Gum are mixed together, the "smooth", unsubstituted regions of the Locust Bean Gum molecules associate with the helical Xanthan structures to produce a matrix that is both stronger than high viscosity xanthan and less rubbery than cross-linked locust bean gum. This process is stimulated by the presence of cations (○).
"Smooth" region of Locust Bean Gum molecule
Cations
Helical Xanthan structure
TIMERx® Drug Delivery System
Drug H-bonds to Polysaccharides
KEY
Dextrose Cations Drug H-bonds

Figure 3 Molecular conformation of a heterodisperse polysaccharide system in the presence of saccharide, drug, and cation. (See color insert.)

IV. RESEARCH AND DEVELOPMENT

A. Formulation Considerations

A number of factors are important in the development of controlled-release dosage forms using the TIMERx technology, including (a) dose of the active drug, (b) solubility of the active drug, (c) polymer ratios (xanthan gum : locust bean gum) (d) active drug : polymer ratio, and (e) bulk excipient selection.

The first two factors, dose and solubility, must be taken into consideration for any drug delivery system. The differentiating factor for the TIMERx system is the working range for each—dose: 4–850 mg (representing approximately 2–70% drug loading); and solubility : insoluble to freely soluble.

The next two factors are unique to the system. The ratio of the polymers controls both the rate and modality of drug release. In addition, the active drug : polymer ratio is important since, similar to other hydrophilic matrix systems, the more polymer that is added to the tablet formulation, the slower the rate of drug release. This effect reaches a maximum beyond which any further addition of polymer has little or no effect.

Finally, the addition of excipients can play an important role in the characteristics of the finished product. For example, materials can be added to promote

Copyright © 2003 Marcel Dekker, Inc.

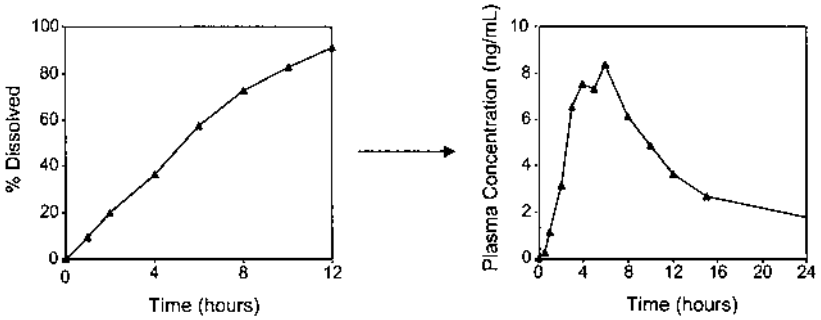


Figure 4 In vitro and in vivo profiles for a product developed using the TIMERx system for a low-dose, highly soluble drug to be delivered at a constant rate for twice-daily dosing.

stability or solubility of the drug and subsequently enhance release from the matrix.

B. System Flexibility

The TIMERx technology is extremely flexible in terms of the types of drugs it is capable of delivering. As mentioned previously, a large range of doses and solubilities is possible. Moreover, a variety of release profile types can be achieved, including first-order, zero-order, and pulsatile release. Figures 4–6 provide three examples to demonstrate the capabilities of the system in which formulations were evaluated both in vitro and in vivo. These cases were examined in which drugs with different physicochemical and pharmacokinetic properties were developed into controlled-release dosage forms. The formulations were evaluated

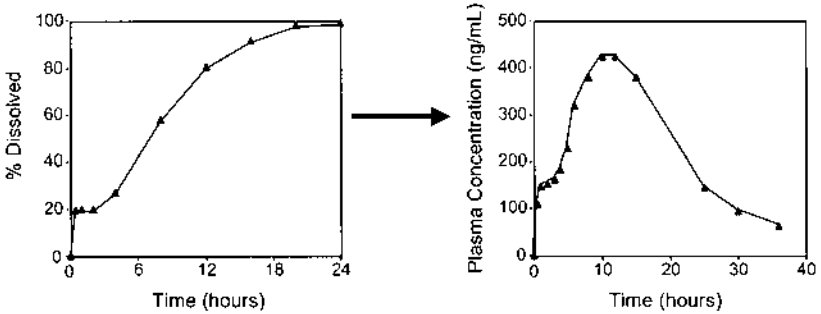


Figure 5 In vitro and in vivo profiles for a product developed using the TIMERx system for a high-dose, highly soluble drug to be delivered at a pulsed rate for once-daily dosing.

Copyright © 2003 Marcel Dekker, Inc.

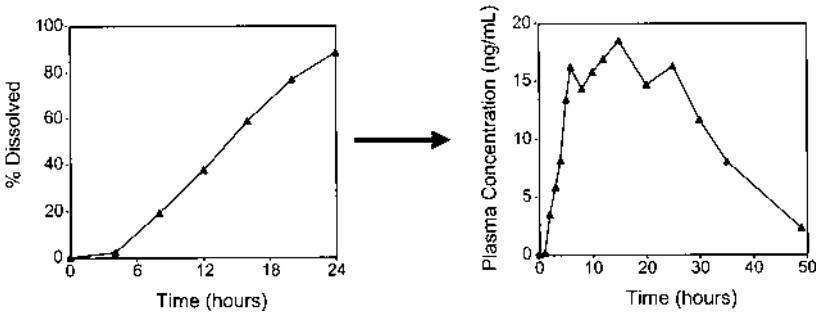


Figure 6 In vitro and in vivo profiles for a product developed using the TIMERx system for a medium-dose, poorly soluble drug to be delivered at a constant rate for once-daily dosing.

in vitro and in vivo and shown to have achieved the desired profiles. The results support the claim that the TIMERx technology is suitble for a variety of drug molecules and release profiles.

C. System Manufacturability

The TIMERx technology offers the additional benefit of ease of manufacture compared to more complicated drug delivery systems. For example, certain formulations have been developed that exhibit similar in vitro and in vivo profiles compared to alternative systems. In these cases, the TIMERx-based products were manufactured using a simple, three-step process involving blending, compressing, and coating. By contrast, the alternate products were developed and manufactured using a complex series of steps that required specialized equipment and personnel. Formulations based on the TIMERx technology have been routinely scaled-up from the laboratory to production.

D. In Vitro–In Vivo Relationships

In vitro–in vivo relationships (IVIVR) have been studied extensively and are used to establish a correlation between the physicochemical properties of a dosage form and its biological performance. IVIVR can be used to (a) serve as a surrogate to bioequivalence testing for scale-up and postapproval changes (b) justify dissolution specifications for quality control purposes, and (c) enhance predictabiltiy of in vivo performance and thus improve product development efficiencies. Extensive work has been done to establish such relationships for products developed using the TIMERx technology in both fasted and fed states. Although many researchers focus solely on the fasted condition, the postprandial

Copyright © 2003 Marcel Dekker, Inc.

state is equally important for controlled-release dosage forms since some systems can exhibit dose dumping. While food effects are well documented, the mechanisms are not well understood. Two critical factors that can affect the absorption, distribution, metabolism, and excretion involve effects on the dosage form and gastrointestinal physiology. When prediction of in vivo behavior in the fed state is attempted, the situation is confounded by the multiplicity of technologies that exist. Therefore, when considering the effects on the dosage form, one must first fully understand the mechanism by which drug is released in the body. Controlled-release systems deliver drugs by diverse mechanisms, and thus can be affected by food in very different ways. Moreover, the effect of food on gastrointestinal physiology is important in understanding such effects. Delayed gastric emptying, increased gastric pH and motility, and decreased polarity of the gastric contents are all known to occur in the fed state. Therefore, significant efforts have been made to develop predictive in vitro tests to provide an understanding of how the dosage form is expected to perform in the body.

In addition, a gamma scintigraphy study was performed using a placebo TIMERx tablet to determine the nature of the wetted core during gastrointestinal transit. The results indicated that the tablet does not disintegrate, but rather slowly erodes as it moves through the gastrointestinal tract. This is an important feature since it suggests that there is no danger of gastrointestinal blockage.

V. SUMMARY

The TIMERx technology is among the leading oral drug delivery technologies. It was originally developed to provide a simple alternative to the more complicated controlled-release systems while overcoming the deficiencies associated with conventional hydrophilic matrices. The technology is one of the most flexible in terms of dealing with drugs with varying physicochemical and pharmacokinetic properties, doses, and desired release profiles. The finished dosage forms can be readily manufactured on standard processing equipment, resulting in ease of technology transfer and cost-effectiveness. In addition, the technology is well protected with more than 90 patents issued worldwide. Several products using the TIMERx system have been approved in the United States and Europe. These features ultimately provide the end-user with the ability to rapidly develop and produce superior oral controlled-release products.

REFERENCES

1. JN Staniforth, AR Baichwal. Synergistically interacting heterodisperse polysaccharides: function in achieving controllable drug delivery. In: MA El-Nokaly, DM Piatt,

Copyright © 2003 Marcel Dekker, Inc.

BA Charpentier, eds. Polymeric Delivery Systems: Properties and Applications. American Chemical Society, 1993, pp. 327–350.
2. AR Baichwal, JN Staniforth. Directly compressible sustained release excipient. US patent 4,994,276, 1991.
3. AR Baichwal, JN Staniforth. Sustained release excipient and tablet formulation. US patent 5,128,143, 1992.
4. AR Baichwal, JN Staniforth. Compressible sustained release solid dosage forms. US patent 5,135,757, 1992.

Copyright © 2003 Marcel Dekker, Inc.

3

MASRx and COSRx Sustained-Release Technology

Syed A. Altaf
Gilead Sciences, Foster City, California, U.S.A.

David R. Friend
Delsys Pharmaceutical, a division of Elan Operations, Inc., Monmouth Junction, New Jersey, U.S.A.

I. INTRODUCTION

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix® technology) and osmotic pumps with laser-drilled holes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients.

Hydrocolloids are often used in formulations to modify or sustain the release of drug from matrix controlled drug delivery systems. A common problem associated with high-viscosity water-soluble polymers is their ability to hydrate. Hydration is even more difficult when these polymers are compressed into solid dosage forms. Tablets containing elevated levels of high-viscosity polysaccharides begin to gel and hydrate, but the hydration oftens stops at a certain point. The core of the tablet remains dry and therefore not all the drug may be released.

Copyright © 2003 Marcel Dekker, Inc.

Depending on other excipients or the amount of the hydrocolloid, tablets composed of high-viscosity polysaccharides can disintegrate quickly, resulting in dose dumping or the immediate release of the drug.

Guar gum, a naturally occurring, highly viscous, water-soluble polysaccharide, is used in the pharmaceutical industry primarily as a disintegrating and binding agent in compressed tablets [1–3]. Guar gum's potential in sustaining the release of water-soluble drugs, such as diltiazem, has recently been published [4,5]. The advantages of guar gum as a sustained-release excipient are its high viscosity, low cost, and commercial availability [6,7]. Guar gum has also been purified and evaluated as an improved pharmaceutical excipient for sustained-release formulations [8].

II. EXPERIMENTAL

For guar-gum-based technologies, all the ingredients except magnesium stearate were mixed together in a V-blender for 10 min. The powder mixture was dry-granulated using a Freund Mini Roller Compactor (pressure = 90 kg/cm^2, feed speed = 12 rpm, and roller speed = 5 rpm). Resulting powder blend ribbons were milled and sieved through screens, retaining granules between 250 μm and 600 μm. The collected granules were mixed with magnesium stearate in a V-blender for 10 min and then compressed into tablets. A wet granulation procedure was also evaluated and used for the optimized diltiazem formulations. In the case of nifedipine formulations, tablets were coated in a pan coater.

For dissolution studies, USP Apparatus II at 50, 100, and 200 rpm paddle speed with simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) was used. Dissolution profiles were reduced to a meaningful set of parameters by fitting the dissolution curves to the Weibull function [9]. Analysis of covariance was performed on the dissolution curves to examine whether differences were significant based on a predetermined α level, which was set at 5%. Statistics were performed using JMP® (Version 3.2.2., SAS Institute, Cary, NC). In the case of nifedipine, dissolution was performed at 100 rpm paddle speed with SIF under yellow light; 0.25% sodium lauryl sulfate (SLS) was added to enhance the solubility of nifedipine and maintain sink conditions. For drug product assay, a validated high-performance liquid chromatography (HPLC) method was used for both drugs.

The GMP manufacturing and stability of the clinical trial materials were conducted at Penn Pharmaceuticals Ltd., Gwent, UK and Pharmaceutics International, Inc., Hunt Valley, MD. Clinical studies were performed by Corning Besselaar Clinical Research Unit, Madison, WI. The plasma samples were analyzed by Hazelton Wisconsin, Madison, WI.

Copyright © 2003 Marcel Dekker, Inc.

III. MASRx TECHNOLOGY

A. Formulation Development

The objective was to assess factors affecting drug release from guar-gum-based once-daily matrix sustained-release formulations (MASRx™). The tablets were designed to hydrate completely into the tablet core. In the process, the tablet core expanded and released the drug in a sustained-release manner.

Guar gum is a natural product that can vary in specifications crop to crop, season to season. To evaluate the effect of varying lots of guar gum on dissolution, formulation A (Table 1) was manufactured with three lots of guar gum obtained from the same manufacturer. The resulting dissolution release rate constants (Table 2) were insignificantly different ($p = 0.98$). The variability among three commercial sources of guar gum was also evaluated by using formulation A. It was shown that guar gum source did not affect diltiazem release (Table 2).

The effect of final powder blend particle size distribution on diltiazem release showed a statistically significant difference in the diltiazem release rate constant as observed from tablets made with 150–600-μm granules compared with those made from 425–600-μm and 250–600-μm granules (Table 2). The difference in drug release is possibly due to the greater percentage of fines in the 150–600-μm size granules, which causes the tablet to hydrate faster leading to rapid gelling of the polymer, which in turn slows the drug release. The diltiazem powder blend was also equilibrated to humidity levels of 11%, 56%, and

Table 1 Summary of the Clinical Trial Formulations Based on MASRx Technology

	Formulations				
Ingredients	A	B	C	D	E
Diltiazem HCl, USP	31.00%	31.00%	31.00%	31.60%	31.60%
Guar gum (Supercol G3-NF)	62.00		62.00	64.60	57.15
Purified guar gum[a] (Supercol G3-NF)		67.00			
Methocel K100LV	5.00			2.50	10.00
Polyethylene oxide (Polyox, MW = 8,000,000)			5.00		
Povidone				0.25	0.25
Stearic acid	2.00	2.00	2.00		
Magnesium stearate, NF				2.00	2.00
Total weight	785 mg	785 mg	785 mg	785 mg	785 mg

[a] See Ref. 8 concerning purified guar gum.

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Summary of the Dissolution Parameters from Guar-Gum-Based Diltiazem Formulation A and the Commercial Dilacor XT Formulation

		b(beta)	d(Td)	K = 1/Td	*p* value
Lot	Lot 1	0.8245	8.6181	0.1162	
	Lot 2	0.8718	7.7822	0.1167	0.98
	Lot 3	0.8471	8.6212	0.1160	
Vendor	Aqualon	0.8245	8.6181	0.1162	
	Meer	0.9662	8.5856	0.1168	0.999
	TIC gums	0.9195	8.5954	0.1194	
Particle size	Less than 106 μm	0.8360	6.0665	0.1648	
	Greater than 150 μm	0.8152	6.3235	0.1581	0.872
	Whole distribution	0.8230	8.1844	0.1222	
Hardness	6 kp	0.8415	7.1947	0.1390	
	9 kp	0.8467	7.6799	0.1302	0.981
	12 kp	0.8230	8.1844	0.1222	
Granule size	425–600 μm	0.8244	8.6181	0.1160	
	250–600 μm	0.7668	8.5269	0.1173	0.621
	150–600 μm	0.6693	15.7700	0.0634	
Relative humidity	11%	0.6811	6.0078	0.1665	
	56%	0.7681	7.8724	0.1270	0.862
	75%	0.7650	8.2545	0.1211	
Paddle speed	Formulation A, 50 rpm	0.9935	8.7374	0.1144	
	Formulation A, 100 rpm	0.9865	7.3990	0.1352	0.831
	Formulation A, 200 rpm	0.9303	5.9415	0.1683	
	Dilacor XR, 50 rpm	1.1648	8.0423	0.1243	
	Dilacor XR, 100 rpm	1.2671	7.1083	0.1407	0.716
	Dilacor XR, 200 rpm	1.2119	4.7412	0.2109	
Stability	Initial	0.9865	7.3990	0.1352	
	1 month	0.9716	6.5471	0.1527	0.979
	3 month	0.9970	7.4006	0.1351	

75% and compressed into tablets to evaluate the effect of relative humidity. The resulting release rate constants show insignificant difference in diltiazem release (Table 2). Likewise, varying tablet hardness (6, 9, or 12 kp) did not significantly affect dissolution of diltiazem (Table 2). The effect of paddle speeds, 50, 100, and 200 rpm (USP Apparatus II), was also evaluated on diltiazem release for both the guar-gum-based and the commercial diltiazem product Dilacor XR®. An insignificant difference in diltiazem release was observed at the 50- and 100-rpm paddle speeds. At 200-rpm paddle speed, dissolution exhibits some differences in diltiazem release at the later time points. Although both formulations showed

Copyright © 2003 Marcel Dekker, Inc.

a qualitative increase in dissolution rate at 200 rpm, these differences were statistically insignificant.

Stability of guar-based tablets was assessed over 3 months at 40°C and 75% relative humidity. The release rate constants for the 1- and 3-month dissolution data for the guar-gum-based diltiazem formulations are shown in Table 2. The results show that the dissolution profiles over the 3 months do not change significantly ($p = 0.979$).

B. Clinical Evaluations

Three guar-gum-based diltiazem formulations (formulation A, B, and C) were selected for clinical trials along with the reference commercial product, Dilacor XR 240 mg. In vitro release profiles of diltiazem from the three guar-gum-based formulations were very similar to those of the commercial product, Dilacor XR (Fig. 1). The three guar-gum-based diltiazem formulations differ slightly in their composition (Table 1). All three guar-gum-based formulations sustained the release of diltiazem in vivo over 24 h nearly identical to Dilacor XR. Plasma diltiazem concentration plots (Fig. 2) indicated that the absorption of diltiazem from all four formulations was fairly constant over a period of 16–24 h postdose. Among the guar-gum-based formulations, formulation A produced plasma con-

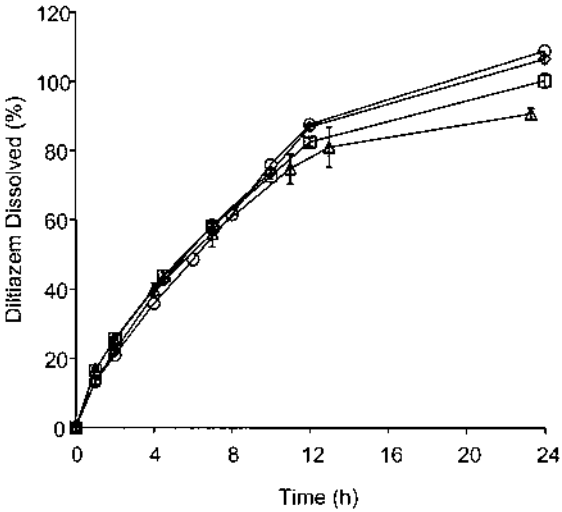


Figure 1 Diltiazem dissolution release profiles of sustained release formulations A (□), B (△), C (◇), and the reference product, Dilacor XR 240 mg (○).

Copyright © 2003 Marcel Dekker, Inc.

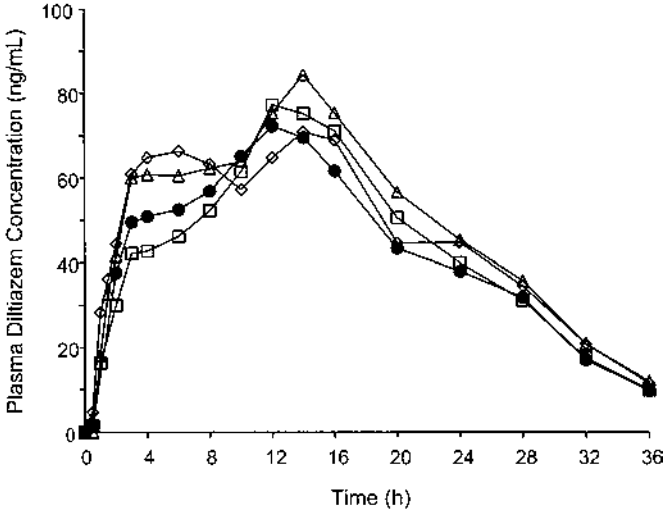


Figure 2 Mean plasma diltiazem concentrations from guar-gum-based formulations A (□), B (△), and C (◇), and the reference product, Dilacor XR 240 mg (●).

centrations most similar to those of Dilacor XR. The physicochemical change resulting from guar gum purification manifests itself with slightly lower variability in C_{max} than the unpurified guar. Table 3 summarizes the pharmacokinetic parameters for the clinical formulations. Based on these data, methods were examined to bring the C_{max} closer to the reference product in both fasted and fed conditions. First, increasing drug release rate over the first 4–6 h followed by a

Table 3 Geometric Mean Pharmacokinetic Parameters and 90% Confidence Intervals (upper, lower) for Initial Diltiazem Formulations

Formulation	$AUC_{(0\text{-}36)}$ (ng/h/mL)	C_{max} (ng/mL)
Dilacor XR	1340	69.5
A	1484	79.0
	(0.91, 1.35)	(0.91, 1.41)
B	1588	83.6
	(0.97, 1.44)	(0.97, 1.49)
C	1599	81.1
	(0.98, 1.45)	(0.94, 1.45)

Copyright © 2003 Marcel Dekker, Inc.

period of slow release compared to the reference product (i.e., fast/slow formulation) was hypothesized. In this case, more drug should be available in the early hours following dosing bringing the C_{max} down at a later time point. The second approach was to decrease the release rate for all time points, i.e., a slower releasing formulation. Based on these two approaches, two new diltiazem formulations were developed (formulations D and E, see Table 1). The in vitro dissolution profiles for the two new formulations are shown in Figure 3. The two optimized formulations were evaluated in a second fed and fasted trial.

All the enrolled subjects (nine and 12 in the fasted and fed studies, respectively) completed the three-period crossover studies. There were no serious adverse events. The mean plasma diltiazem concentrations following oral administration of Dilacor XR, formulations D and E to fasted and fed subjects are plotted to Figure 4. Absorption of diltiazem from formulations D and E was similar to the reference product in both the fasted and fed state. The geometric means used for bioequivalence analysis of D and E with the fasted and fed data are given in Tables 4 and 5, respectively. Based on the data collected under fed and fasted conditions, formulations D and E released diltiazem similar to the referenced product, Dilacor XR.

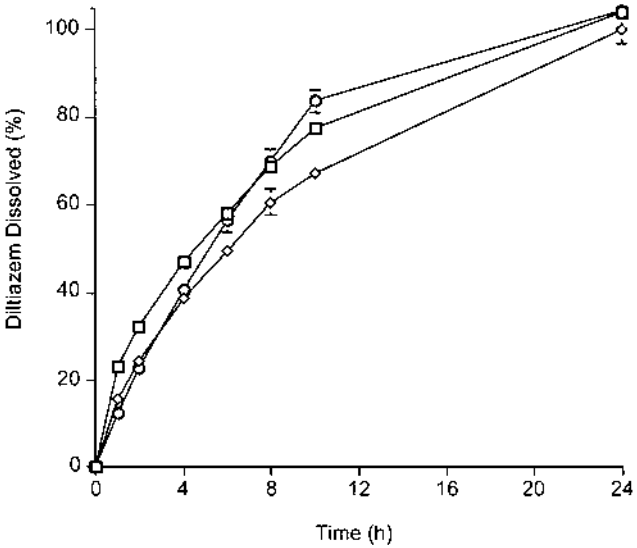


Figure 3 Diltiazem dissolution release profiles of optimized sustained-release formulations D (□) and E (△) in reference to Dilacor XR 240 mg (○) (data are mean ± s.d., $n = 12$).

Copyright © 2003 Marcel Dekker, Inc.

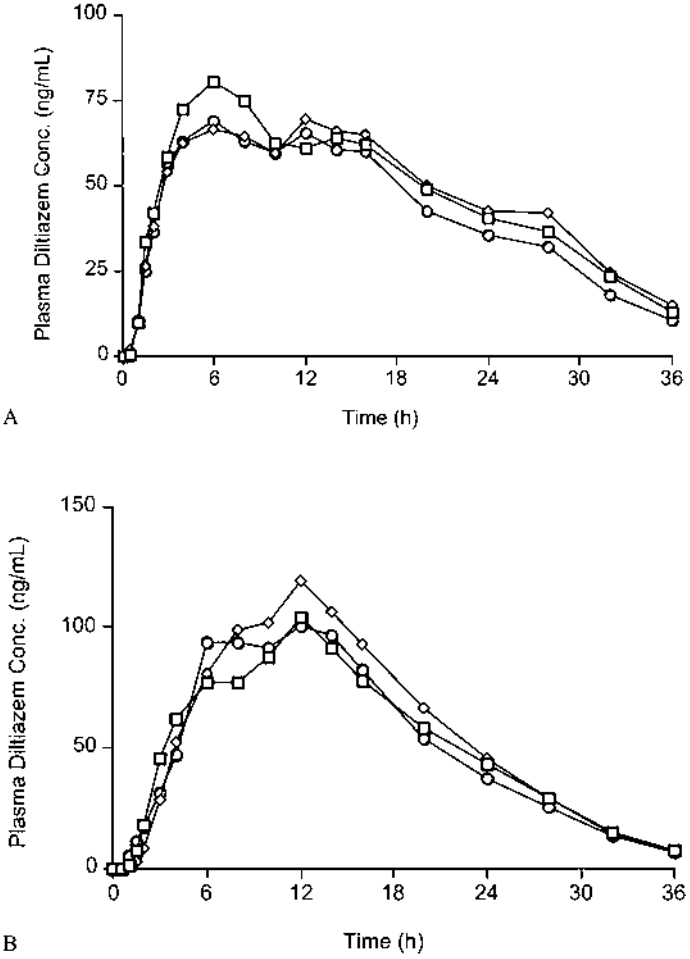


Figure 4 Mean plasma diltiazem concentrations from formulations D (□), E (△), and Dilacor XR 240 mg (○) in fasted ($n = 12$) (panel A) and fed ($n = 9$) subjects (panel B).

IV. COSRx TECHNOLOGY

A. Formulation Development

Formulations based on constant sustained-release matrix (COSRx™) technology can also be developed using guar gum as a major rate-controlling polymeric material. Depending on the solubility of the drug, low- or high-viscosity guar gum

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Geometric Means, Ratios, and 90% Confidence Intervals of Diltiazem for Formulations D and E Under Fasted Conditions

Parameter	Mean		Ratio (%) (T/R)	90% confidence level	
	Test	Reference		Lower	Upper
Test (formulation D): Reference (Dilacor XR)					
$AUC_{(0\text{-}36)}$ (ng/h/mL)	1545	1553	99.5	0.87	1.13
$AUC_{(0\text{-}\infty)}$ (ng/h/mL)	1654	1702	97.2	0.85	1.11
C_{max} (ng/mL)	77.5	76.0	101.9	0.86	1.21
Test (formulation E): Reference (Dilacor XR)					
$AUC_{(0\text{-}36)}$ (ng/h/mL)	1342	1553	86.4	0.76	0.98
$AUC_{(0\text{-}\infty)}$ (ng/h/mL)	1470	1702	86.3	0.76	0.99
C_{max} (ng/mL)	73.3	76.0	96.4	0.81	1.14

can be used. The formulation involves a guar-gum-based tablet and a combination of water-soluble and water-insoluble polymeric tablet coat. When the tablet is placed in a dissolution medium, there is slow diffusion of water through the polymeric wall leading to swelling and gelation of the guar gum/drug core. As the hydration progresses, the tablet continues to swell until the wall breaks, forming a sandwich-like structure. The release of drug proceeds primarily out of the sides of the tablet as it passes through the intestinal tract. The tablets provide a nearly

Table 5 Geometric Mean Diltiazem Ratios of Formulations D and E Under Fed Conditions

Parameter	Mean		Ratio (%) (T/R)
	Test	Reference	
Test (formulation D): Reference (Dilacor XR)			
$AUC_{(0\text{-}36)}$ (ng/h/mL)	1992	1753	113.6
$AUC_{(0\text{-}\infty)}$ (ng/h/mL)	1984	1809	109.7
C_{max} (ng/mL)	122.7	108.1	113.5
Test (formulation E): Reference (Dilacor XR)			
$AUC_{(0\text{-}36)}$ (ng/h/mL)	1798	1753	102.6
$AUC_{(0\text{-}\infty)}$ (ng/h/mL)	1854	1809	102.5
C_{max} (ng/mL)	119.1	108.1	110.2

Copyright © 2003 Marcel Dekker, Inc.

zero-order drug release following a programmed period of delayed drug release. A variety of drug release profiles can be obtained by adjusting the coating thickness and/or the matrix core composition.

To achieve a constant zero-order matrix sustained release formulation (COSRx) for a poorly water-soluble drug such as nifedipine ($\leq$10 μg mL^{-1}), a low-molecular-weight guar gum (Tico-LV) was used. Channeling agents such as water-insoluble silicon dioxide or water-soluble lactose were used to enhance the porosity of the matrix aiding in the dissolution of drug. A combination of water-soluble (Eudragit RL PO) and water-insoluble polymers (Eudragit RS PO), in the ratio of 1:9 (RL:RS), was used as coating material (2% w/w). The combination produced a lag time in drug release of 2 h, similar to that observed with the reference nifedipine product, Procardia XL 30 mg. Various other polymeric coating materials can be used such as ethylcellulose, cellulose acetate, and other esters. A summary of the formulations used as clinical trial materials is provided in Table 6.

A constant zero-order nifedipine release with a lag time of 2 h was achieved with formulation A using silicon dioxide as a porosity enhancer (Fig. 5). The nifedipine release profile was adjusted by simply modifying the tablet weight to match the release profile of a commercially available Procardia XL 30-mg tablet (Fig. 5). The tablet configuration and the percent drug content were kept constant with a proportional decrease in the remaining ingredients. The increase in release rate is probably due to larger drug surface area to tablet size ratio.

Constant release profiles were also achieved by using lactose monohydrate as a porosity enhancer. Small amounts of low-viscosity carboxyvinyl polymer (Carbopol 974 P, NF) were also added to maintain the nearly constant zero-order nifedipine release (Fig. 6).

Table 6 Summary of the Clinical Trial Formulations Based on COSRx Technology

	Formulation		
Ingredient	A	B	C
Nifedipine, USP	10	10	10
Guar gum, low viscosity (Tic-LV NF)	43	35	35
Polyvinylpyrrolidone (Plasdone K-25)	16.5	16.5	16.5
Silicon dioxide (Syloid 244 FP)	30	0	0
Lactose monohydrate (Fast Flo)	0	35	32
Carboxyvinyl polymer (Carbopol 974P)	0	3	6
Magnesium stearate, NF	0.5	0.5	0.5
Eudragit RL/RS Coating (1:9)	2	2	2

Copyright © 2003 Marcel Dekker, Inc.

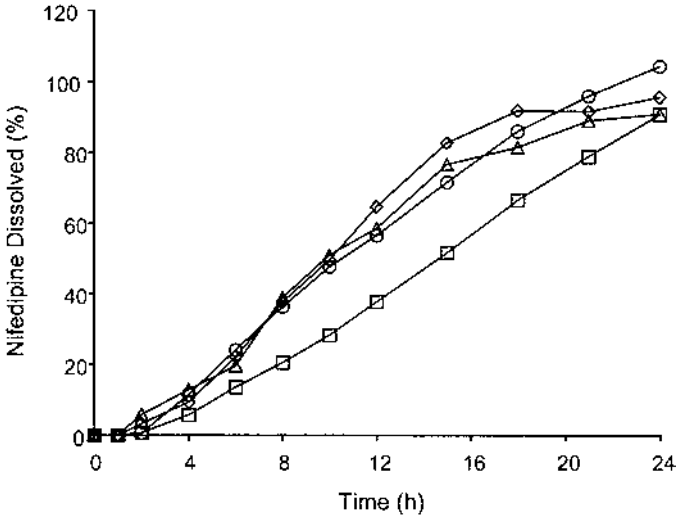


Figure 5 Effect of adjusted tablet weight on nifedipine release from guar-gum-based formulation A, 300 mg (□), 275 mg (△), 250 mg (◇), and Procardia XL 30 mg (○).

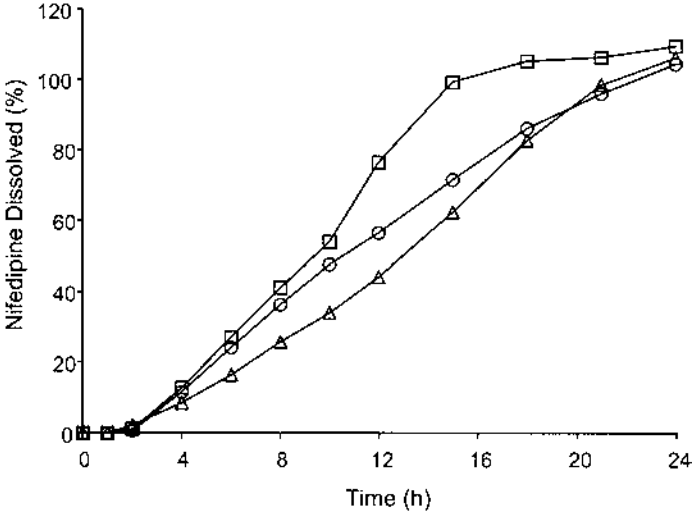


Figure 6 Effect of varying concentrations of Carbopol on nifedipine release from guar-gum-based formulations B (□) and C (△) compared to Procardia XL 30 mg (○).

Copyright © 2003 Marcel Dekker, Inc.

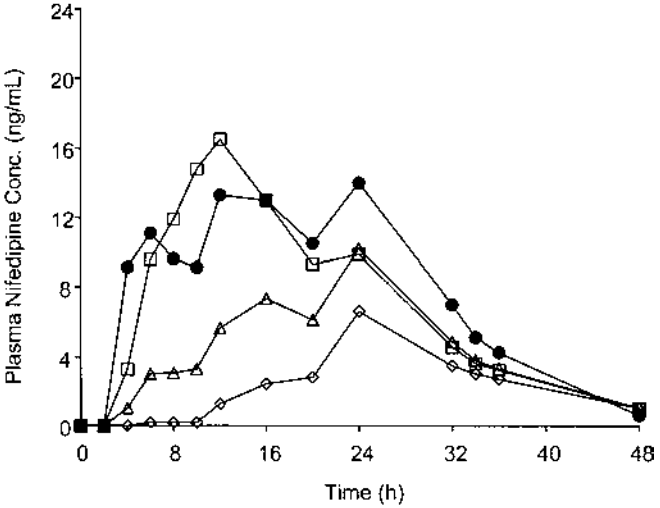


Figure 7 Mean plasma nifedipine concentrations over time following oral administration of guar-gum-based formulations A (◇), B (△), and C (□) and the reference product Procardia XL (●).

B. Clinical Evaluation

Twelve subjects (fasted) received a single dose of each nifedipine formulation containing 30 mg drug with 240 mL water in a random order. All 12 subjects completed the four-period crossover study. Plasma was analyzed for nifedipine by a validated HPLC method. All three guar-gum-based formulations sustained the release of nifedipine in vivo over 24 h (Fig. 7). Among the guar-gum-based formulations, formulation B produced plasma concentrations most similar to those of Procardia XL 30 mg.

V. CONCLUSIONS

Guar gum has shown potential as a sustained-release matrix based upon diltiazem and nifedipine in vitro and in vivo results. The effect of different lots of guar gum and different manufacturers on diltiazem release was insignificant. Also, dissolution of diltiazem from guar gum formulations was nearly independent of stir speed under normal dissolution conditions. The stability of guar-based formulations under stressed conditions was also established. The guar-gum-based formulations provided sustained diltiazem and nifedipine release similar to the reference products, Dilacor XR and Procardia XL, respectively.

Copyright © 2003 Marcel Dekker, Inc.

ACKNOWLEDGMENTS

HPLC analysis of stability samples as performed by Susan Larrabee. Acknowledgments are extended to Dr. Walter Doll and Philip Fowler at the University of Kentucky for their assistance with the dissolution studies.

REFERENCES

1. AM Sakr, HM Elsabbagh. Correlation of water absorption with the disintegration effectiveness of guar gum. Pharm Ind 37:457–459, 1975.
2. EM Rudnic, CR Rhodes, JF Bavitz, JB Schwartz. Some effects of relatively low levels of eight tablet distintegrants on a direct compression system. Drug Dev Ind Pharm 7:347–358, 1981.
3. MZ Iqbal, M Amin, NA Muzaffar. Comparative evaluation of guar gum as disintigrating agent. J Pharm 1:17–34, 1979.
4. SA Altaf, KL Yu, J Parasrampuria, DR Friend. Guar gum-based sustained release diltiazem. Pharm Res 15:1196–1201, 1998.
5. K Yu, M Gebert, SA Altaf, D Wong, DR Fiend. Optimization of sustained-release diltiazem formulations in man by use of an in-vitro/in-vivo correlation. J Pharm Pharmacol 50:845–850, 1998.
6. K Yu, D Wong, J Parasrampuria, DR Friend. In: HG Brittain, ed. Analytical Profiles of Drug Substances and Excipients. Vol. 24. Orlando, FL: Academic Press, 1996, pp. 397–442.
7. AM Goldstein, E Alter, JK Seaman. Guar gum. In: Industrial Gums, Polysaccharides and Their Derivatives. 2nd ed. New York: Academic Press, 1973, pp. 303–321.
8. MS Gebert, DR Friend. Purified guar galactomannan as an improved pharmaceutical excipient. Pharm Dev Technol 3:315–323, 1998.
9. F Langenbucher. Parametric representation of dissolution-rate curves by the RRSBW distribution. Pharm Ind 38:474–477, 1976.

Copyright © 2003 Marcel Dekker, Inc.

4

Procise: Drug Delivery Systems Based on Geometric Configuration

Sham K. Chopra
Savit Consulting Inc., Brampton, Ontario, Canada

I. INTRODUCTION

Procise™ is an oral modified-release drug delivery system comprised of a compression-coated core whose geometric configuration controls the release profile of drugs. By varying the geometry of the core, the profile of the drug release can be adjusted to follow zero order, first order, or a combination of these orders. The system can also be designed to deliver two drugs at the same time, each having a different release profile.

Procise was developed by Glaxo Canada Inc.* in 1991. The company has filed patent applications on a worldwide basis to protect the Procise intellectual property. Patents for this technology have been granted in Europe and the United States. Patent applications in Japan and Canada are pending. These patents will expire in November 2012.

Glaxo Canada Inc. has granted AlthoTech Pharma† a limited sole worldwide license to develop, manufacture, and market non–Glaxo Wellcome molecules in Procise delivery systems. Glaxo Canada Inhc. has reserved the right to use the technology for its own molecules.

---

* Current name and address: Glaxo SmithKline, 7333 Mississauga Road, Mississauga, ON, L5N, 6L4, Canada.

† AlthoTech Pharma Inc., 310 Glen Manor Drive West, Toronto, ON, M4E 2X7, Canada.

Copyright © 2003 Marcel Dekker, Inc.

II. HISTORICAL DEVELOPMENT

It is believed that to obtain a constant drug level in the blood a drug delivery system must release drug at a constant rate. To achieve this constant rate, several mechanisms (osmosis, diffusion, and dissolution) and dosage form modifications have been employed [1,2]. The current systems based on diffusion and dissolution mechanisms do not provide a true zero-order release rate. The release of drug from these systems occurs either at a first-order rate or as a square-foot function of time with a declining release profile. The osmotically driven systems release drug at a constant rate as long as the concentration of the osmotic agent in the system is at the saturation point. When the concentration of the osmotic agent falls below the saturation point, the release rate declines parabolically toward zero [3].

Attempts have been made to achieve constant rates of drug release by controlling the surface area of tablets [4–6]. However, such systems have not been successful either due to improper design of the system or due to yet-undeveloped manufacturing technology. It is not surprising therefore that the marketing exploitation of these patents has never been attempted. Therefore, there was a need to develop an oral solid-dose drug delivery system that could be designed to provide any desired drug release profile and manufactured on a commercial scale with relative ease.

III. DESCRIPTION OF THE TECHNOLOGY

The system consists of a core (Fig. 1) that contains uniformly dispersed drug and has a hole in the middle. A slowly permeable inactive coat surrounds all of the surface of the core except the surface of the cylindrical face (Fig. 2, item 3). The drug release occurs only from the cylindrical face, whose surface area dictates the rate of release of drug.

A. Mechanism of Release

The mechanism of release of drug from this uniquely designed dosage form can be diffusion based or dissolution based.

1. Theory of Procise System Based on Dissolution Mechanism

The release rate, dm/dt, of a drug from a compressed soluble disc, when governed by dissolution, can be expressed as:

$$dm/dt = A(dx/dt)C \tag{1}$$

Copyright © 2003 Marcel Dekker, Inc.

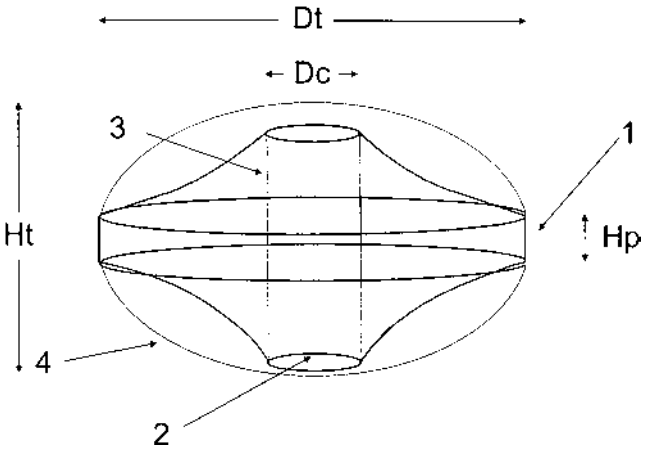


Figure 1 Configuration of the zero-order release active core used in Procise: (1) cylindrical face, (2) cylindrical bore, (3) outer wall of cylinder, (4) inert coat. Dt, diameter of the core; Dc, diameter of the cylinder; Ht, thickness at the cylinder; Hp, thickness at the cylindrical face.

where A is the surface area, C is the concentration of the drug in the core, and dx/dt is the mass erosion rate. The above equation predicts a constant dissolution rate if the surface area is kept constant, active substance is uniformly distributed within the tablet, and the mass erosion rate is uniform. In reality, however, the rate of dissolution is not a simple function of surface area alone. It is a complex function of changing size and the shape of the disc itself, as well as fluid dynamics of the adjacent solvent layer [7]. Nevertheless, a constant dissolution rate can be expected provided the surface area is properly controlled [8].

2. Theory of Procise Based on Diffusion Mechanism

The release of drug from a solid matrix by diffusion can be represented by the following equation:

$$dq/dt = -D\,A\,dc/dr \tag{2}$$

where q is the mass of drug being transferred, t is the time, c is the drug concentration, r is the diffusion path length, A is the area for the mass transport, and D is the diffusion coefficient of the drug. According to the above equation, the drug release rate decreases as the diffusion path length, r, increases. As r cannot be kept constant, one way to keep the release rate constant is to increase the area

Copyright © 2003 Marcel Dekker, Inc.

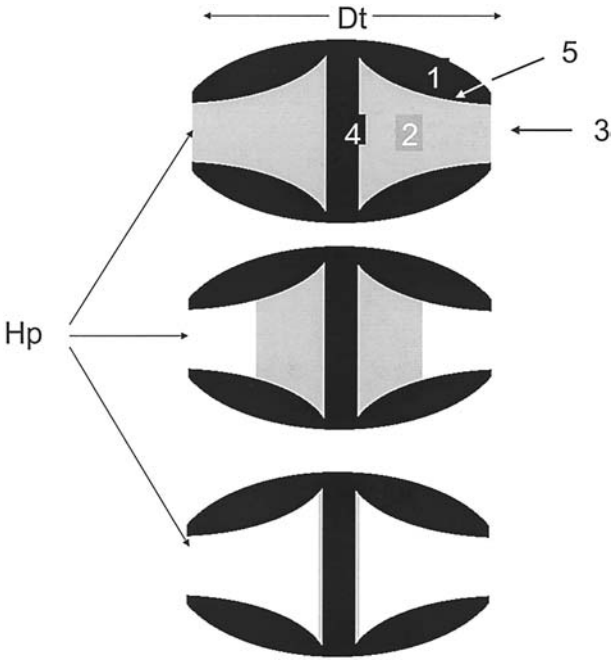


Figure 2 Schematic cross-sectional views at various stages of dissolution testing of a Procise formulation designed to release drug at a constant rate: (1) coat, (2) active soluble core, (3) cylindrical face, (4) central pillar attached to the upper and lower face of the coat, (5) core/coat interface. Dt, diameter of the tablet core; Hp, thickness of the cylindrical face.

of available diffusion source to compensate for the increase in diffusion distance of drug transport.

B. Configurations

3. Procise System Based on Dissolution Mechanism

The schematic cross-sectional diagram of the Procise system that releases drug at a constant rate is shown in Figure 2. The geometric configuration of the core (Fig. 1) in this system (Fig. 2) is such that its thickness increases when moving toward the cylinder from the periphery. In fact, the thickness of the core is inversely proportional to its diameter. As a result, the surface area, $Hp \times Dt \times \pi$ of its cylindrical face does not change even when the diameter of the core is reduced to the diameter of the cylinder whose surface area is given by $Ht \times Dc$

Copyright © 2003 Marcel Dekker, Inc.

$\times \pi$, where *Hp* is the height of the cylindrical face, *Dt* is the diameter of the core, *Ht* is the height of the cylinder, and *Dc* is the diameter of the cylinder.

When coated, the coating material fills the cylinder bore and therefore acts as a central pillar joining the coat on the upper and lower face of the core (Fig. 2, item 4). The cylindrical face is the only exposed surface of the core.

The mechanism of drug release from a constant-rate Procise (Fig. 2) has been described previously [9]. Briefly, when exposed to the dissolution medium, the cylindrical face (Fig. 2, item 3) of the core dissolves. As a result, *Dt* decreases while *Hp* increases, i.e., as the diameter of the core decreases, the cylindrical face with increasing height is continuously exposed. Throughout the dissolution process, the product of height and diameter remains constant and hence the release rate of drug remains constant.

By varying the geometry of the core, various drug release profiles can be achieved. As an example, the core shown in Figure 3 provided 20% release of a drug within the first 15 min and the remaining 80% was released at a constant rate (Fig. 4, Tablet B). This profile was achieved by designing the core geometry in such a way that the exposed surface area of its cylindrical face that dissolves in the first 15 min is larger than that which remains constant for the remainder of the dissolution process. The system can also accommodate two drugs, each having a different release profile. Such a system will have one soluble drug incorporated in its coat and the other drug in its core.

2. Procise System Based on Diffusion Mechanism

The appearance of the diffusion-based Procise system (Fig. 5) is the same as that of the dissolution-based system (Fig. 2). However, the geometric configuration of the diffusion-based core (Fig. 5, item 2) is different from that of the dissolution-

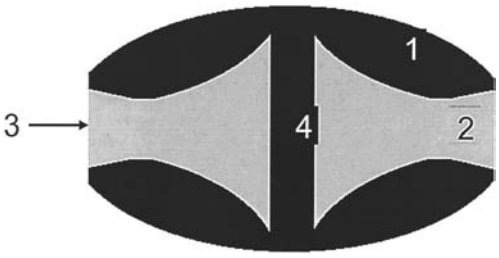


Figure 3 Schematic cross-sectional view of a Procise formulation designed to release 20% of the drug in first the 15 min and the remaining 80% of the drug at a constant rate: (1) coat, (2) active soluble core, (3) cylindrical face, i.e., the dissolution front, (4) central pillar attached to the upper and lower face of the coat.

Copyright © 2003 Marcel Dekker, Inc.

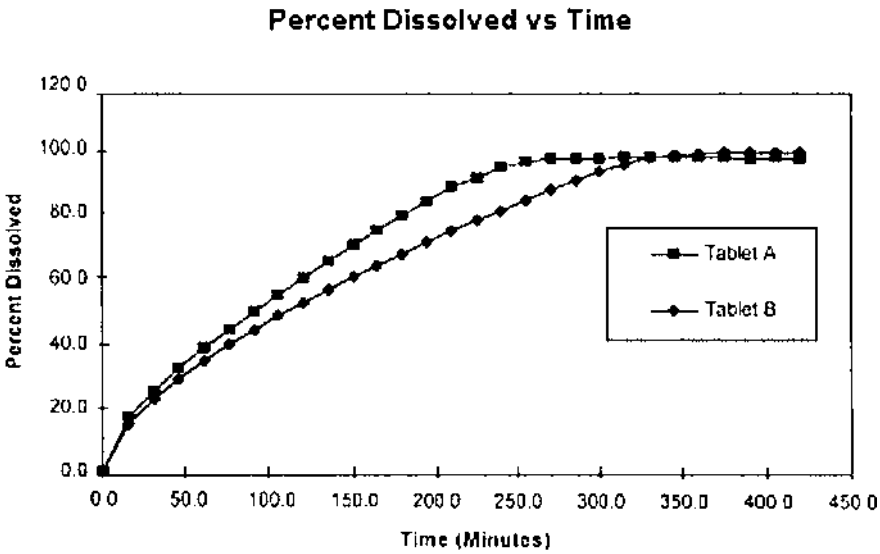


Figure 4 Dissolution profile of Tablet A and Tablet B in simulated fluid (USP) without enzyme.

based core (Fig. 2, item 2). In the diffusion-based zero-order system, the surface area of the diffusion front, which is the cylindrical face and the release surface initially, increases when moving toward the cylinder from the periphery (Fig. 5). In fact, the increase in the surface area, $Hp \times Dt \times \pi$, of the diffusion front is made to counter the increase in diffusion path length, r, as the dissolution process proceeds and the diffusion front moves away from the release surface. The increase in surface area of the diffusion front is effected by the increase in the thickness of the core when moving toward the cylinder from the periphery.

IV. MANUFACTURING PROCESS

Manufacturing processes for the diffusion- and the dissolution-based systems are very similar. However, the diffusion-based cores are composed of soluble and insoluble components whereas dissolution-based cores are composed of soluble components only. Granules for the cores are prepared using conventional, dry or wet granulation methods and cores are compressed on a conventional press fitted with core-rod punches.

Copyright © 2003 Marcel Dekker, Inc.

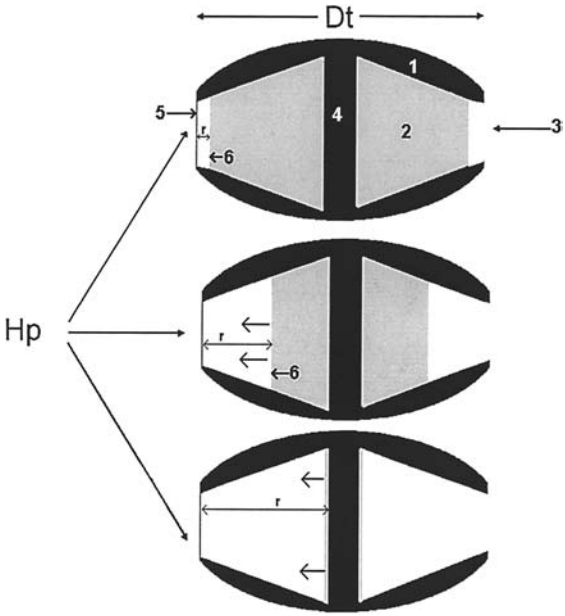


Figure 5 Schematic cross-sectional views at various stages of dissolution testing of a diffusion-based Procise formulation designed to release drug at a constant rate: (1) coat, (2) active soluble core, (3) cylindrical face, (4) central pillar attached to the upper and lower face of the coat, (5) release surface, which is cylindrical face (3) and initial dissolution front, (6) diffusion front. Dt, diameter of the tablet core; Hp, thickness at the cylindrical face; r, diffusion path length.

The precompressed cores are compression-coated using a core coater fitted with a set of specially designed tooling for placing cores precisely in the dyes. The sequence of the compression coating process is shown in Figure 6. Coating formulations for both the systems are composed of insoluble pharmaceutically acceptable polymers and soluble plasticizers or soluble compounds.

V. DEVELOPMENT AND OPTIMIZATION OF TECHNOLOGY

During the early development trials, it became abundantly clear that erosion of the dissolution cores must occur only from the exposed surface, which is the cylindrical face, and the erosion must be uniform to achieve drug release profiles as per theoretical predictions. The drug release profile of a dissolution-based Pro-

Copyright © 2003 Marcel Dekker, Inc.

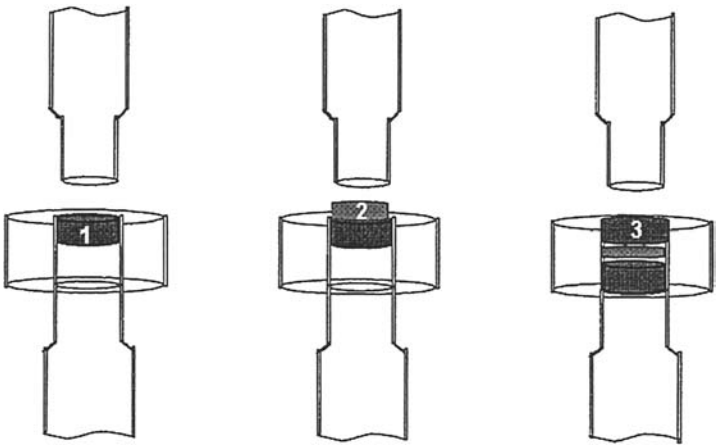


Figure 6 Sequence of compression coating process: (1) coating granules for upper face of the tablet, (2) core, (3) coating granules for lower face of the tablet.

cise system, identified as Tablet A in Figure 4, reveals that the core dissolved in 4 h instead of 5 h predicted from the tablet geometry and formulation. Visual and microscopic examination did not reveal any abnormalities in the tablets. Examination of the cores, after removal of the coat from the tablets that had been in the dissolution medium for 1–2 h, revealed that their sides along the core/coat interface had hydrated (Fig. 7). Whether the water was penetrating along the core/coat interface or through the coat was determined using the nuclear magnetic

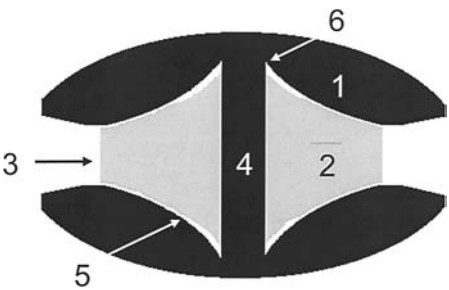


Figure 7 Schematic cross-sectional view of Tablet A, approximately 1 h after the tablet was placed in a dissolution bath; (1) coat, (2) active soluble core, (3) cylindrical face, (4) central pillar attached to the upper and lower face of the coat, (5) hydration of the core/coat interface, (6) intersection of central pillar and coat.

Copyright © 2003 Marcel Dekker, Inc.

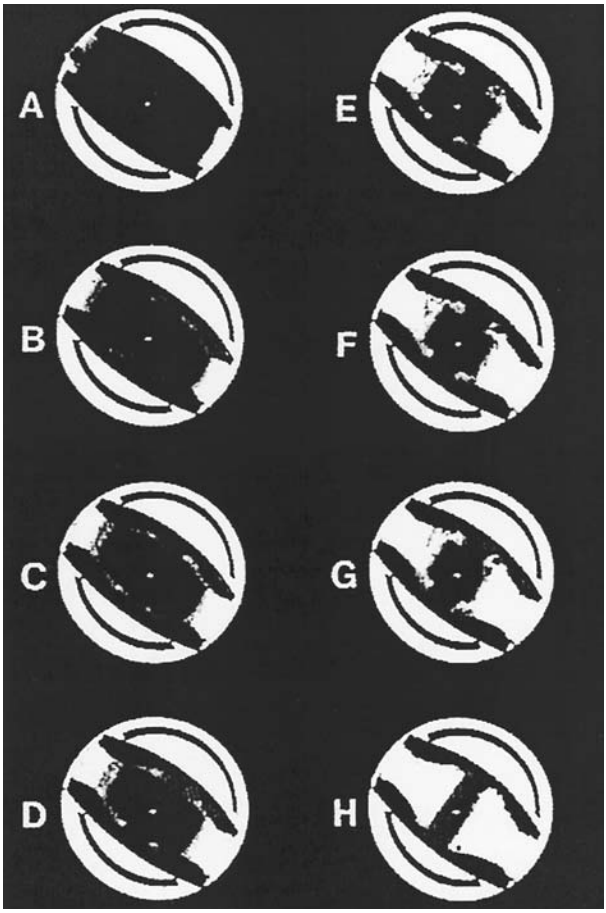


Figure 8 NMR images of Tablet A at various stages of dissolution: (A) 15 min, (B) 1 h, (C) 2 h, (D) 3 h, (E) 5 h, (F) 6 h, (G) 7 h, (H) 14 h.

resonance (NMR) technique [10]. The NMR images (Fig. 8) of the tablet taken at different intervals of time during the dissolution in a static simulated gastric fluid without enzyme shows that the dissolution of the core was occurring not only from the cylindrical face but also from the two sides of the core. The images depicted in Figure 8 are in the plane region and should follow the changes in the shape of the core that are schematically drawn in Figure 3.

In the images (Fig. 8), the white areas indicate high water concentration, the black areas indicate minimal or no unbound water concentration, and the gray

Copyright © 2003 Marcel Dekker, Inc.

areas indicate intermediate water concentration. The dark ring around the tablet is due to plastic support used to hold the tablet in a fixed position.

The hydration of the core for Tablet A is clearly visible in the 15-min image (Fig. 8). The sign of hydration of the core also appears at the core coat interface as seen in the 1-h image (B) in Figure 8. The most surprising observation was that in this image, the whole core/coat interface on both sides of the tablet had hydrated, suggesting that the penetration of the medium occurred through the coat. This observation is supported by the fact that the highest water concentration

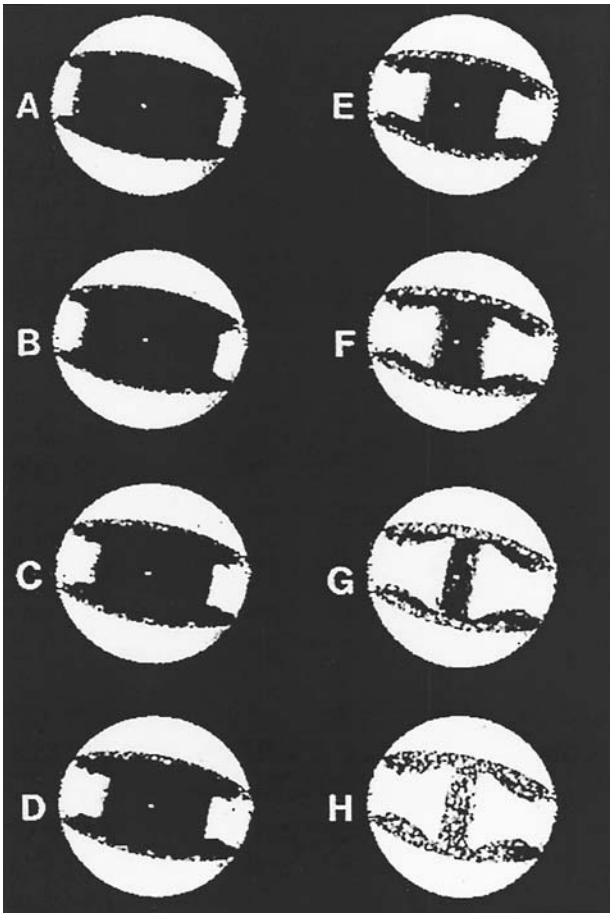


Figure 9 NMR images of Tablet B at various stages of dissolution: (A) 20 min, (B) 1 h, (C) 2 h, (D) 3 h, (E) 5 h, (F) 7 h, (G) 9 h, (H) 16 h.

Copyright © 2003 Marcel Dekker, Inc.

as indicated by the whiteness of the area was present at the intersection of the central pillar and the coat. This intersection is the point where the coat is the thinnest (Fig. 7, item 6). Although the coat was formulated to allow absorption of water to weaken the structure of the coat, and effect its disintegration at some time point after all of the drug is released, the penetration of the medium through the coat to the core at such an early stage of the dissolution process was unexpected. The observation through NMR imaging pointed to the porousness of the coat.

The coat was reformulated to retard the rate of penetration of the dissolution medium into the coat to prevent hydration of cores from the sides. The dissolution plot of Tablet B (Fig. 4) indicates that the drug release from this tablet with the modified coat formulation was complete in 5 h, which is in excellent agreement with the predicted time. The NMR images (Fig. 9) of Tablet B showed no sign of water along the core/coat interface throughout the core dissolution process.

Careful inspection of the images of Tablet B reveals that the water begins to penetrate the coat at some point earlier than 1 h but at a much lower rate than in the case of Tablet A. The penetration is not quite complete at 9 h when all the core has dissolved away. These images demonstrate that a properly optimized formulation of Procise behaves as conceptualized.

VI. IN VITRO STUDIES

Several in vitro studies have been carried out to demonstrate that the drug release profile from Procise follows the theoretical predictions. Release profiles of two Procise formulations, one based on the dissolution mechanism and the other based on the diffusion mechanism, are shown in Figure 10 and Figure 11, respectively. The dissolution studies were carried out in water using USP apparatus 2.

The plot in Figure 10 shows a zero-order release profile for a dissolution-based Procise formulation of labetalol hydrochloride over a 10-h period. Nearly all of the drug is released in that time at a rate of 9.59%/h. The correlation coefficient of the straight-line relationship is 0.9952. The plot in Figure 11 displays dissolution behavior of a diffusion-based Procise formulation of salbutomol sulfate. All of the drug is released in 6.5 h. The release is rapid (~40%) in the first 1.5 h followed by slow release at a constant rate of 0.06857 mg/h.

VII. IN VIVO STUDIES

The in vivo drug release behavior of dissolution-based Procise system has been evaluated using a gamma scintigraphy technique in six healthy male subjects. Neutron-activated samarium-153 and ytterbium-175 were used to label the core

Copyright © 2003 Marcel Dekker, Inc.

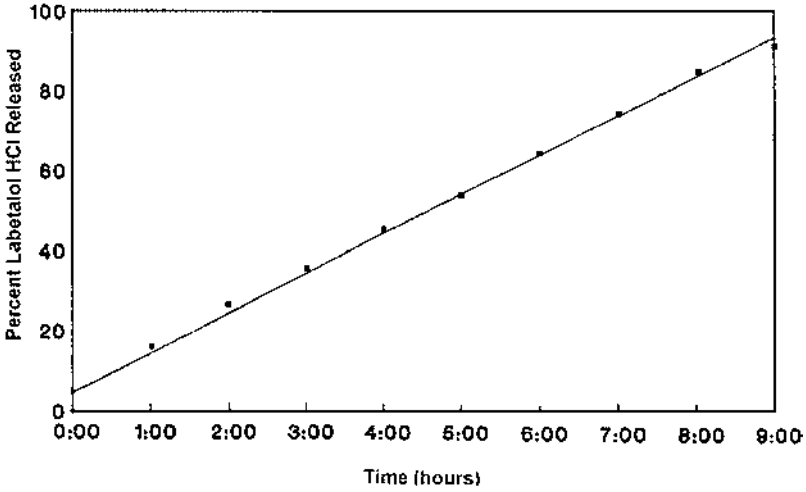


Figure 10 Release profile of the dissolution-based Procise formulation of labetalol hydrochloride in water.

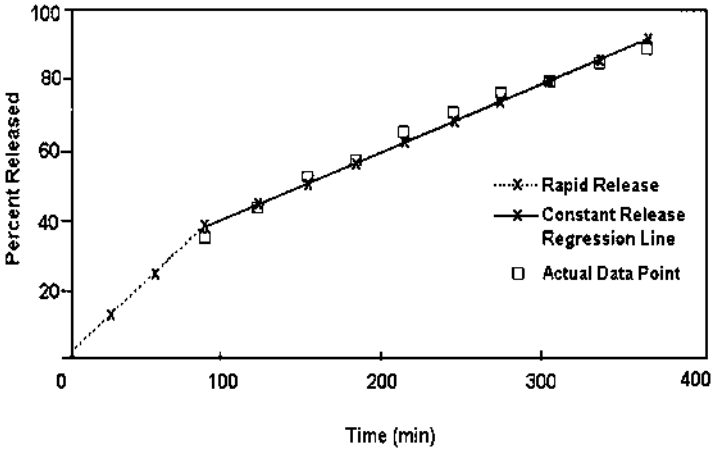


Figure 11 Release profiles of diffusion based Procise of salbutamol sulfate in water.

Copyright © 2003 Marcel Dekker, Inc.

and the coat, respectively, of a placebo tablet. The tablet showed no apparent physical changes after neutron bombardment. In vitro core dissolution time of 4.5 h remained unchanged after neutron activation.

The mean in vitro release duration for ^{153}samarium was 4.1 ± 1.6 h, which compared well with 4-5 h dissolution duration in vitro. Considering that during the in vivo dissolution process, cores were located in the stomach where tablets face more turbulence than in a dissolution vessel, this is an example of excellent in vitro/in vivo correlation.

VIII. REGULATORY ISSUES

No regulatory issues were raised with the three human bioavailability studies carried out to date.

IX. COMPETITIVE ADVANTAGE

Procise has the competitive advantage over other oral delivery systems as the drug release profile can be easily modulated in a predictable manner simply by changing the geometric configuration of its core. No other drug delivery system currently on the market can claim this feature.

X. CONCLUSIONS

Except for oral delivery systems based on osmosis, there are no controlled-release systems on the market that can claim to follow true zero order for the delivery of oral drugs. A lag time is usually associated with osmotic systems, coated diffusion matrices, and coated dissolution matrices before the drug is released. There is no lag with Procise systems. Other salient features of the system are:

Complete drug release from dissolution-based Procise systems.
No intact residue is left in the body as opposed to many diffusion-based matrices, which leave a "ghost residue."
Utilization of compression coating process, which does not require solvents.
No fear of dose dumping as the system's core itself is slow dissolving.
Minimal effect of hydrodynamic conditions prevailing in the stomach as only the peripheral face of the core is exposed.
The system can be easily manufactured on a commercial scale.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. H-W Hui, JR Robinson, VHL Lee. Design and fabrication of oral controlled release drug delivery systems. In: Controlled Drug Delivery Fundamentals and Applications. 2nd ed. New York: Marcel Dekker, 1987, Chapter 9.
2. F Theeuwes. Osmotic system for the control and delivery of agent over time. US patent 4,111,202, 1978.
3. F Theeuwes, D Swanson, P Wong, P Bonsen, V Place, K Hiemlich, KC Kwan. Elementary osmotic pump for indomethacin. J Pharm Sci 72:253, 1983.
4. D Stephenson, J Spence. Prolonged release and oral pharmaceutical tablets and their manufacture. UK patent 1,022,171, 1966.
5. A Reid. Shaped tablets. US Patent Number 3,279,995, 1966.
6. RB DePrince. Disc-like sustained release formulations. US patent 4,663,147, 1987.
7. FJ Rippie, JR Johnson. Regulation of dissolution rate by pellet geometry. J Pharm Sci 58:428, 1969.
8. D Brooke, RJ Washkuhn. Zero-order drug delivery systems: theory and preliminary testing. J Pharm Sci 66:159, 1979.
9. SK Chopra, AK Nangia, D Lee, T Molloy. Controlled release device. European patent 0,542,364 A1, 1993.
10. BJ Fahie, A Nangia, SK Chopra, CA Fyfe, H Grondey, A Blazek. Use of NMR imaging in the optimization of a compression-coated regulated release system. J Control Rel 51:179–184, 1998.

Copyright © 2003 Marcel Dekker, Inc.

5
RingCap Technology

David A. Dickason and George P. Grandolfi
Alkermes, Inc., Cincinnati, Ohio, U.S.A.

I. INTRODUCTION

RingCap is a patented, oral controlled-release drug delivery system. The dosage form is a capsule-shaped matrix tablet to which bands of insoluble material are applied circumferentially to the surface of the tablet (Fig. 1). These bands modify the release of drug from the tablet through the control of surface area [1,2]. In general, the release of drug from RingCap tablets is proportional to the surface area exposed to the dissolution media. This surface area changes over time as the area around the bands becomes hydrated and erodes creating new surface area. This new surface area can decrease, remain constant, or even increase with time. The exposed surface area is controlled by the number, width, and placement of bands of insoluble material applied to the tablets.

II. HISTORICAL DEVELOPMENT

RingCap was developed to address the continuing need for improved oral controlled-release drug delivery systems. The intent was to provide a delivery system with reliable and reproducible drug release characteristics, but also a simple and cost-effective system that could be manufactured with conventional solids-processing equipment.

Copyright © 2003 Marcel Dekker, Inc.

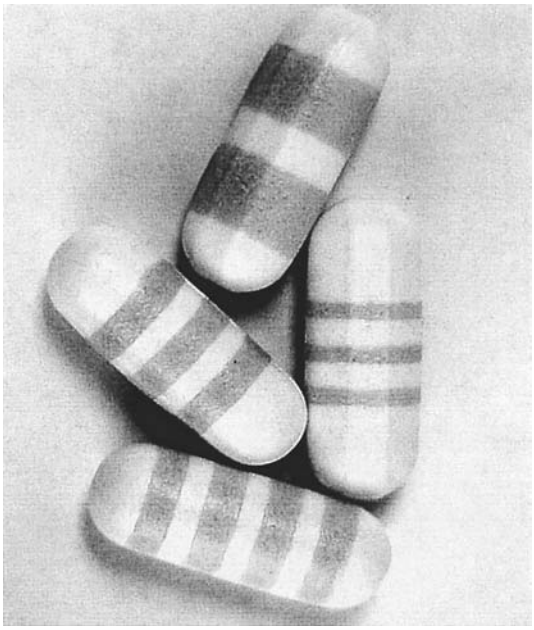


Figure 1 RingCap tablets.

III. DESCRIPTION OF THE TECHNOLOGY

A. Drug Release

The RingCap system is based on the principle that the rate at which a drug is released from an erodible matrix is proportional to the surface area exposed to surrounding liquid over time. As shown schematically in Figure 2, the release rate of drug from a conventional matrix tablet decreases proportionately over time. A typical release profile for acetaminophen formulated in a conventional matrix tablet is shown in Figure 3. With RingCap tablets, however, new surface areas is exposed during the erosion process (Fig. 4). As a result, the rate at which drug is released can be designed to decrease, remain constant, or even increase with time. The specific configuration of number, width, and placement of the bands on the RingCap tablet determines the release profile. Figure 5 shows the release profile for acetaminophen RingCap tablets with four 2-mm bands.

A proprietary mathematical model, developed to predict the release of drug from RingCap tablets, allows for the design of specific banding configurations that target the desired release profile prior to laboratory experimentation, thereby shortening development time.

Copyright © 2003 Marcel Dekker, Inc.

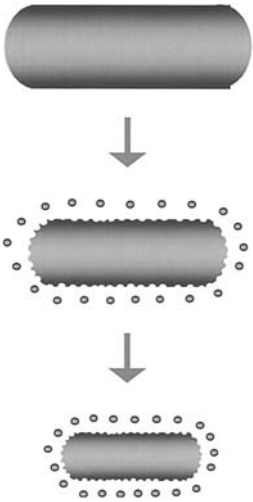


Figure 2 Schematic erosion of a conventional matrix tablet. (See color insert.)

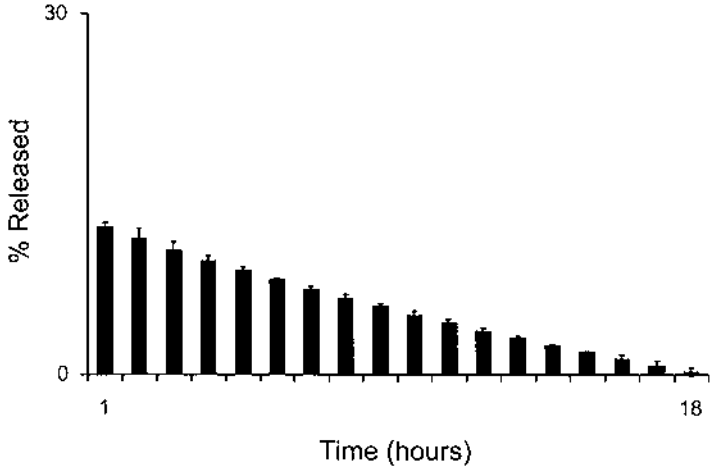


Figure 3 Release from 750-mg acetaminophen matrix tablets (no bands.)

Copyright © 2003 Marcel Dekker, Inc.

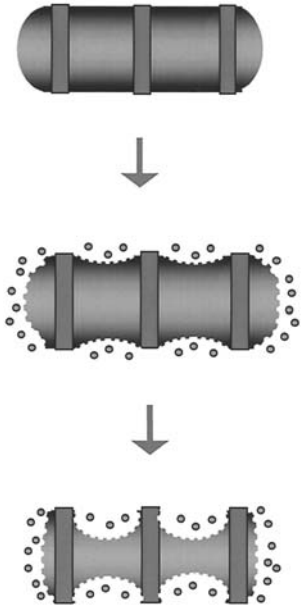


Figure 4 Schematic erosion of a RingCap tablet. (See color insert).

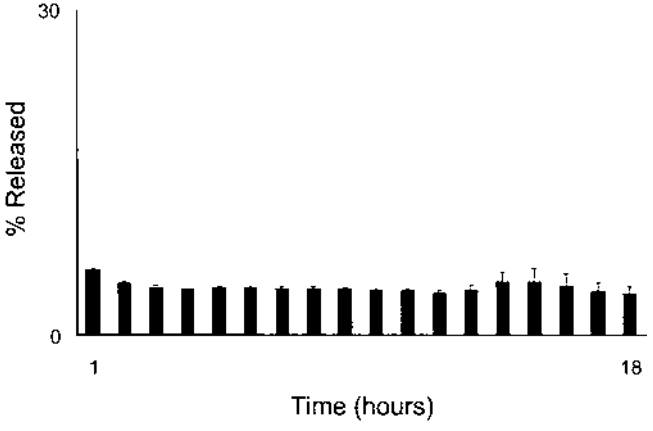


Figure 5 Release from 750-mg acetaminophen RingCap tablets (four 2-mm bands).

Copyright © 2003 Marcel Dekker, Inc.

B. Formulation and Manufacturing

RingCap tablets are manufactured using a patented combination of readily available manufacturing techniques and equipment. The matrix core tablet can be prepared by multiple techniques such as low- or high-shear wet granulation, fluid-bed granulation, or dry blending. Capsule-shaped tablets are compressed using high-speed tabletting equipment. A film coat is applied to the matrix tablets to prepare the surface for the application of bands. The banding material for RingCap tablets is selected from a group of polymers that are insoluble and impermeable. The banding formulation may contain plasticizers, colorants, or other additives depending on the specific application. Conventional capsule banding equipment (modified to apply multiple bands) is employed to apply the bands around the circumference of the matrix tablets.

IV. RESEARCH AND DEVELOPMENT

A. Technical Development

Acetaminophen was selected as a model drug to challenge various parameters of the RingCap system, particularly the number, width, and placement of bands on the surface of tablets [3]; 750-mg acetaminophen matrix tablets (24.2 $\times$ 7.7 mm capsule-shaped) were used in all studies. Various band configurations were evaluated for in vitro release using a USP Type III dissolution apparatus.

A comparison of acetaminophen tablets with different numbers and widths of bands indicated that the rate of release and total amount released in 18 h decreased with increasing number of bands and width of bands. The placement of bands on the surface of acetaminophen tablets also affected the release rate. A comparison of RingCap tablets with two 5-mm bands separated by either a 1- or 3-mm gap demonstrated that, although the tablets had the same exposed surface area, the tablets had statistically different release profiles.

The combined effect of number, width, and placement of bands was evaluated using two groups of RingCap tablets: tablets with two 4-mm bands and tablets with four 2-mm bands. The two groups had significantly different banding configurations, but the same exposed surface area. The results of this evaluation showed that the percent of acetaminophen released in each hour (over 18 h) was similar; however, the release profiles were not statistically correlated to each other. Hence, drug release profiles from the RingCap system depend significantly on the specific banding configuration.

The proprietary mathematical model predicts drug release by using the erosion rate of the matrix core tablet and the effect of the various banding parameters, notably the number, width, and placement of bands. The mathematical model was challenged in numerous studies by comparing the predicted release profiles

Copyright © 2003 Marcel Dekker, Inc.

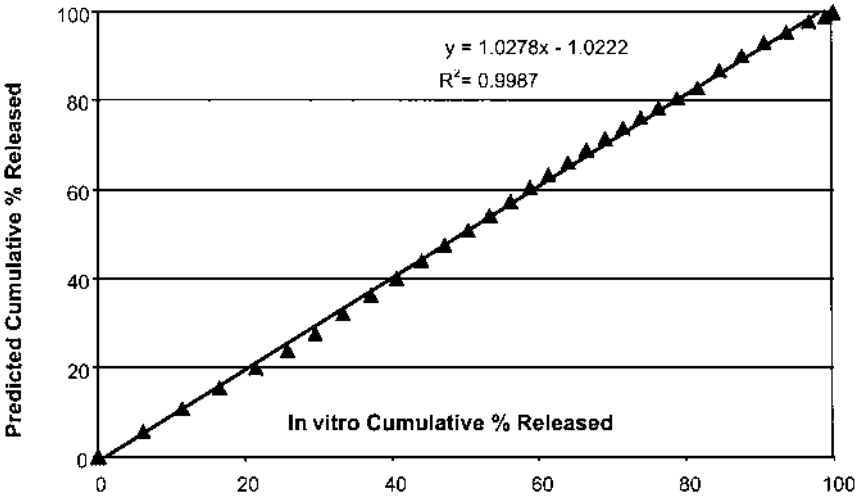


Figure 6 In vitro dissolution versus model predicted for 750-mg acetaminophen RingCap tablets with two 4-mm bands.

to the actual in vitro dissolution data. In each case, the profiles were significantly correlated ($p < 0.001$). Figure 6 shows a representative correlation for 750-mg acetaminophen tablets with two 4-mm bands.

B. Clinical Studies

A critical aspect in the development of a novel drug delivery technology is the demonstration of in vivo performance. For the RingCap system, a randomized, single-dose, three-way, crossover study was conducted in 12 healthy adult human volunteers (eight males, four females) using acetaminophen as a model drug [4]. Acetaminophen meets the criteria as a highly soluble, highly permeable Class I drug according to the Biopharmaceutics Classification System [5]. The three acetaminophen dosing arms in the study included: a 750-mg RingCap tablet (with two 4-mm bands), a 750-mg unbanded matrix tablet, and a commercially available immediate-release dosage form (two 325-mg tablets). A 1-week washout period was included between doses.

The results of this human study showed highly significant differences ($p < 0.001$) among the three formulations for each of the nine pharmacokinetic parameters examined. A comparison of the fraction released and fraction absorbed for the RingCap tablets indicated a Level A in vitro–in vivo correlation [6]. In addition, the mathematical-model-predicted release of acetaminophen from the Ring-

Copyright © 2003 Marcel Dekker, Inc.

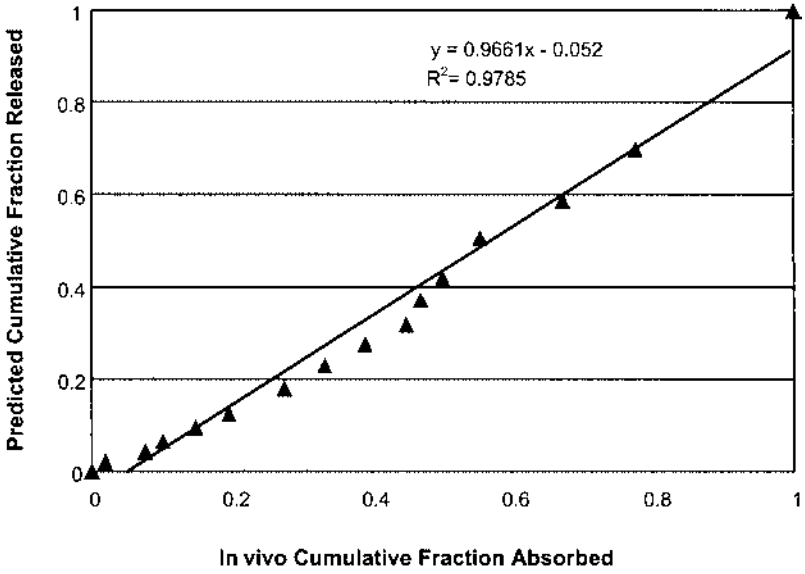


Figure 7 In vivo mean fraction absorbed versus model predicted release for 750-mg acetaminophen RingCap tablets with two 4-mm bands.

Cap tablets was compared to the in vivo fraction absorbed. As shown in Figure 7, a significant correlation was demonstrated. This comparison demonstrates that once an in vitro–in vivo correlation is established, the mathematical model can be used to predict in vitro release profiles and the resulting in vivo plasma concentrations.

V. REGULATORY ISSUES

No anticipated regulatory barriers are associated with the RingCap system. All formulation excipients, including the banding polymer, have been previously demonstrated as acceptable for oral use. In addition, all manufacturing processes use conventional equipment commonly employed for solid oral dosage forms.

VI. TECHNOLOGY POSITION/COMPETITIVE ADVANTAGE

RingCap is differentiated from other oral-controlled release technologies by the availability of a proprietary mathematical model used to predict the release of

Copyright © 2003 Marcel Dekker, Inc.

drug and shorten development time, the use of conventional materials and processes, the relative ease and cost-effectiveness of manufacturing, and the distinctive appearance of the final dosage form.

A proprietary mathematical model is used to predict in vitro drug release from RingCap tablets. The mathematical model enables feasibility and development studies to be accelerated by determining the necessary banding configuration for a desired drug release profile prior to the initiation of laboratory experiments. Once an in vitro–in vivo correlation is established, the mathematical model can also be used to predict in vitro release profiles and the resulting in vivo plasma concentrations.

The RingCap system uses conventional matrix tablet excipients and formulations. It is adaptable to a wide range of drug concentrations and solubilities. RingCap tablets are manufactured using a patented combination of conventional tablet processing and capsule banding technologies that can be easily integrated into existing manufacturing lines. Since there is no need for specialty manufacturing, which often requires outsourcing activities, RingCap offers a cost-effective technology that allows an innovator company to maintain control of quality, cost of goods, and market supply.

The RingCap system creates a distinctive appearance to the final dosage form, which provides opportunity for brand recognition of the innovator product. This recognition may offer a competitive marketing advantage.

VII. FUTURE DIRECTIONS

Future evolution of the RingCap system will include additional surface barrier configurations, polymer matrix core systems, multilayered tablets, and combinations with other conventional controlled-release technologies.

ACKNOWLEDGMENTS

The in vivo human study was conducted at the Drug Research Laboratory, Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee, Memphis, TN.

REFERENCES

1. PS-L Wong, DE Edgren, LC Dong, VJ Ferrari. Active agent dosage form comprising a matrix and at least two insoluble bands. US patent 5,534,263, 1996.

Copyright © 2003 Marcel Dekker, Inc.

2. PS-L Wong, DE Edgren, LC Dong, VJ Ferrari. Banded prolonged release active agent dosage form. US patent 5,667,804, 1997.
3. D Dickason, G Grandolfi, M Leenellett. An in vitro study of the effect of band configuration on the release profile of RingCap tablets. Int Symp Control Rel Bioact Mater 27:435–436, 2000.
4. J Dalton, D Dickason, G Grandolfi, E Rotty, M Leenellett, A Straughn, M. Meyer. An in vivo human pharmacokinetic study comparing RingCap tablets and matrix tablet. Int Symp Control Rel Bioact Mater 27:437–438, 2000.
5. GL Amidon, H Lennerhas, VP Shah, JR Crison. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 12:413–420, 1995.
6. D Dickason, G Grandolfi, E Rotty, M Leenellett, J Dalton. An in vitro–in vivo correlation from a RingCap human pharmacokinetic study. Int Symp Control Rel Bioact Mater 27:439–440, 2000.

Copyright © 2003 Marcel Dekker, Inc.

6

Smartrix System: Design Characteristics and Release Properties of a Novel Erosion-Controlled Oral Delivery System

Horst G. Zerbe
Smartrix Technologies Inc., Kirkland, Quebec, Canada

Markus Krumme
LTS Lohmann Therapie-Systeme AG, Andernach, Germany

I. INTRODUCTION

Controlled-release tablets are oral dosage forms from which the active drug is released over an extended period of time with the aim of decreasing the dosing frequency and reducing peak plasma concentrations, thereby improving patient compliance. Mostly because of low manufacturing costs and ease of application, tablets continue to be a preferred dosage form for controlled-release applications. As a single-unit dosage form, however, controlled release tablets have several therapeutic disadvantages. As shown by Nelson [1] and Münzel [2] and more recently by Bechgaard [3] and Davis [4]. The residence time of single-unit dosage forms in the gastrointestinal tract varies considerably, which may greatly affect the absorption of the active drug. A failure of the mechanism controlling the release of the drug could cause "dose dumping," which might pose a safety risk for the patient.

Typically, controlled- or modified-release tablets are designed as matrix systems, and the release of the drug from the dosage form may be described by Higuchi's $\sqrt{t}$ law. This assumes that the surface area that is available for the

Copyright © 2003 Marcel Dekker, Inc.

release of the drug remains unchanged. A number of attempts have been made to modify the release profile by modifying the surface area of the dosage form. McMullen [5] and more recently Bayomi [6] describe a geometric approach for zero-order release of drugs dispersed in an inert matrix. In both cases, a quasi-linear release profile is accomplished by an erosion-controlled increase of the surface area. Or, as in the case of erosion-controlled polymer embeddings, erosion may become the sole factor controlling the drug release [7].

II. MULTIPLE-LAYERED TABLETS

In recent years, the interest in multiple-layered tablets as an oral controlled-release system has increased. Multiple-layered tablets have some obvious advantages compared to conventional tablets. They are commonly used to avoid chemical incompatibilities of formulation components by physical separation, and release profiles may be modified by combining layers with different release patterns, or by combining slow-release with immediate-release layers.

Conte and Maggi [8] have described an oral controlled-release tablet called Geomatrix, which is based on the multilayered-tablet concept. Functionally, the product represents a swellable matrix. The swelling of the drug-containing layer causes an increase of the surface area and therefore an increase of the amount of drug released per time interval. The outer cover layers control the diffusion of the drug from the core.

Other examples of oral controlled- or modified-release products involving the multiple-layered tablet concept have been described by Qui et al. [9], Yang

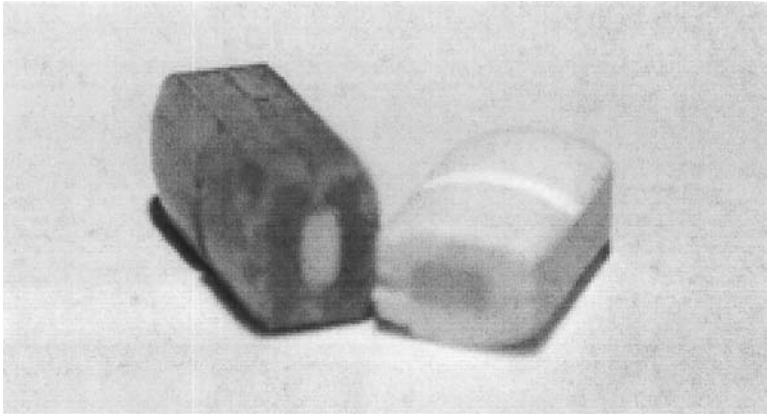
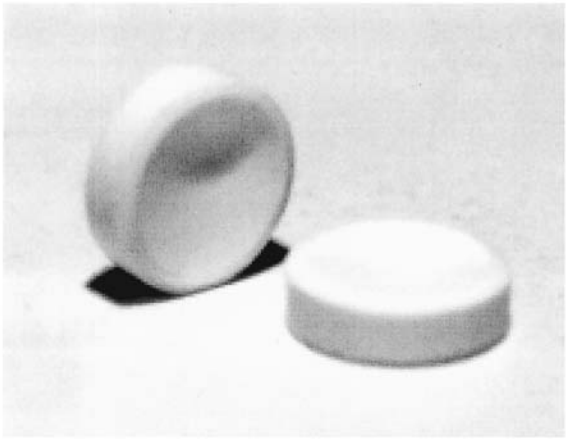


Figure 1 Dry-coated tablet.

Copyright © 2003 Marcel Dekker, Inc.

A.



B.

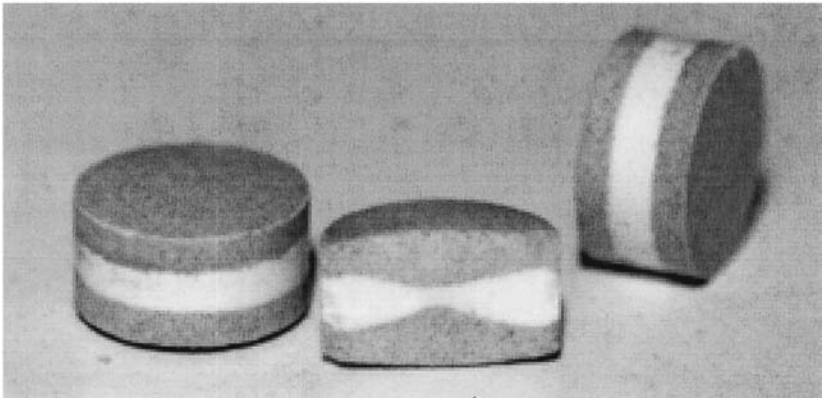


Figure 2 (A) Isolated core matrix layer of a Smartrix tablet. (B) Intact and cross-sectioned Smartrix tablets.

Copyright © 2003 Marcel Dekker, Inc.

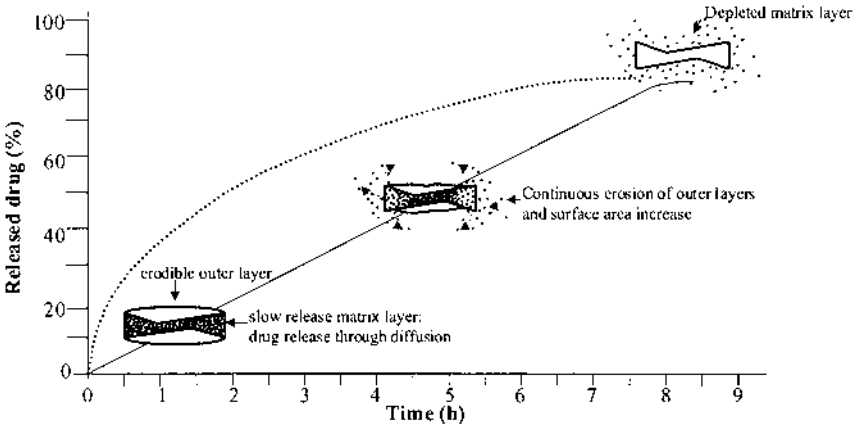


Figure 3 Release profile from core matrix alone and from three-layered Smartrix tablet.

and Fassihi [10], Abraham and Shirwaikar [11], Nangia et al. [12], and Chidambaram et al. [13].

If the core layer of multilayered tablet is completely covered by a surrounding layer, the product is commonly being referred to as a dry-coated tablet. This technique is often used to avoid sugarcoating of a hygroscopic core, but has been replaced to some extent by film coating techniques. Dry-coating techniques have been suggested to produce scored controlled-release tablets (Fig. 1).

Complex multilayered tablets are multilayered tablets with differently shaped layers. The shape of the outer layers depends on the shape of the core tablet (Fig. 2A and 2B). Cremer and Asmussen [14] and Cremer [15,16] first introduced the concept of complex multilayered tablets to achieve zero-order release from matrix-based systems. The Smartrix® system ("smart matrix") is based on the principle that the geometric design of the drug-containing core, in combination with slowly eroding cover layers, provides for quasi-linear release of the drug. The core itself, when not covered by the eroding layers, shows a release profile typical for an inert, porous plastic matrix. However, when the core is covered with erodible layers, the controlled erosion of these outer layers causes a steady increase of the surface area that is available for the release of the drug and provides for a linear release of the drug (Fig. 3).

III. MANUFACTURING TECHNOLOGY

The procedure for manufacturing complex multilayered tablets is illustrated in Figure 4. It involves the following steps: (1) dosing of the bottom layer, (2)

Copyright © 2003 Marcel Dekker, Inc.

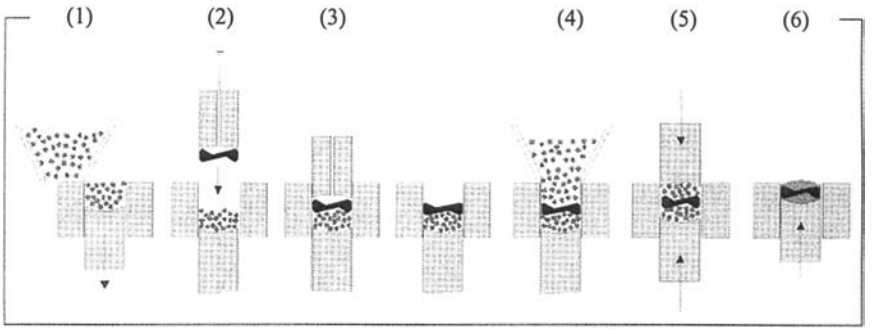


Figure 4 Manufacturing scheme for complex multilayered tablets.

transfer of the prepressed core, (3) insertion into the die, (4) dosing of the top layer, (5) final compression, and (6) ejection. The manufacturing of the matrix cores is performed in a separate step and is usually performed on a regular rotary press. Since the cover layers play a critical role in the drug release mechanism, their weight, thickness, and compaction need to be tightly controlled during the final compression. The process requires specialized equipment that involves transfer punches for the transfer and exact positioning of the core in the die (Fig. 5). The technical concept was introduced by Korsch et al. [17,18]. Today, Smartrix tablets are produced on a high-speed, 48-punch rotary press that was specifically designed for this product.

A. Theoretical Considerations

Smartrix tablets contain the drug suspended in an inert porous plastic matrix. The cumulative amount of drug Q released from the matrix at time t can be described by Higuchi's $\sqrt{t}$ law [19]:

$$Q(t) = (D*\varepsilon/\tau - (2c - \varepsilon*c_s)*c_s)^{0.5} *t^{0.5} \quad (1)$$

where:

D = the diffusion coefficient in the dissolution medium
ε = the porosity of the matrix
τ = the tortuosity of the matrix
c = the initial concentration of drug in matrix
c_s = the solubility of the drug in the dissolution medium

Copyright © 2003 Marcel Dekker, Inc.

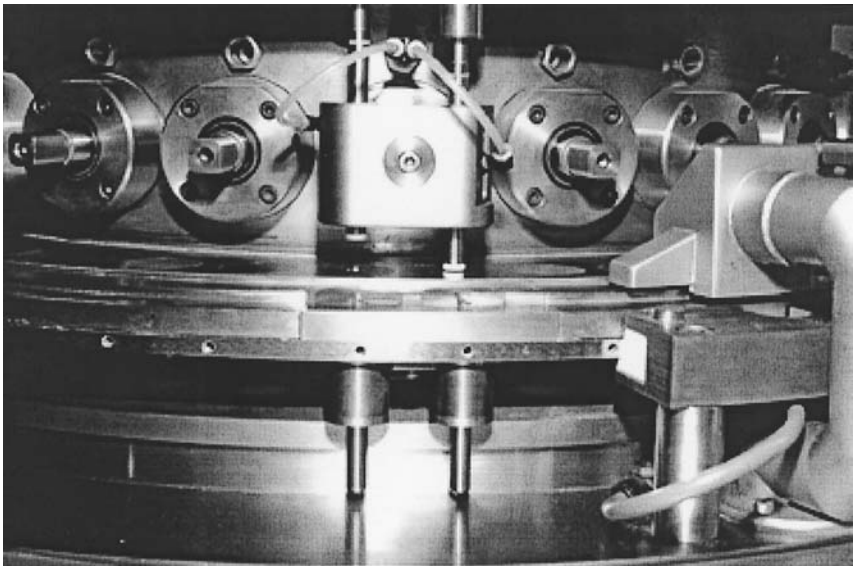


Figure 5 Rotary press used for production of Smartrix tablets with transfer punch.

For a given core layer, the above parameters can be assumed to be constant:

$$K_1 = (D*\varepsilon/\tau - (2c - \varepsilon*c_s)*c_s)^{0.5} \quad (2)$$

and hence

$$Q(t) = k_1*t^{0.5} \quad (3)$$

[The assumption that ε and τ are constant is not entirely correct. Since the porosity increases with the increasing depletion of the matrix, ε and τ correctly should be treated as time-dependent functions $\varepsilon(t)$ and $\tau(t)$.] Release profiles following this model show a curvature typical for matrix systems. The release profile for $k = 20$ in Figure 6A practically resembles that of a matrix-controlled system, because a k value of 20 means that the rate of erosion of the cover layers has no noticeable effect on the overall release rate.

The core layer of a Smartrix tablet is covered by two additional layers, which initially limit the surface area A that is available for the release of the drug. The total amount of drug released at time t from that system could be described by Eq. (4):

$$m(t) = Q(t)*A(t) \quad (4)$$

Copyright © 2003 Marcel Dekker, Inc.

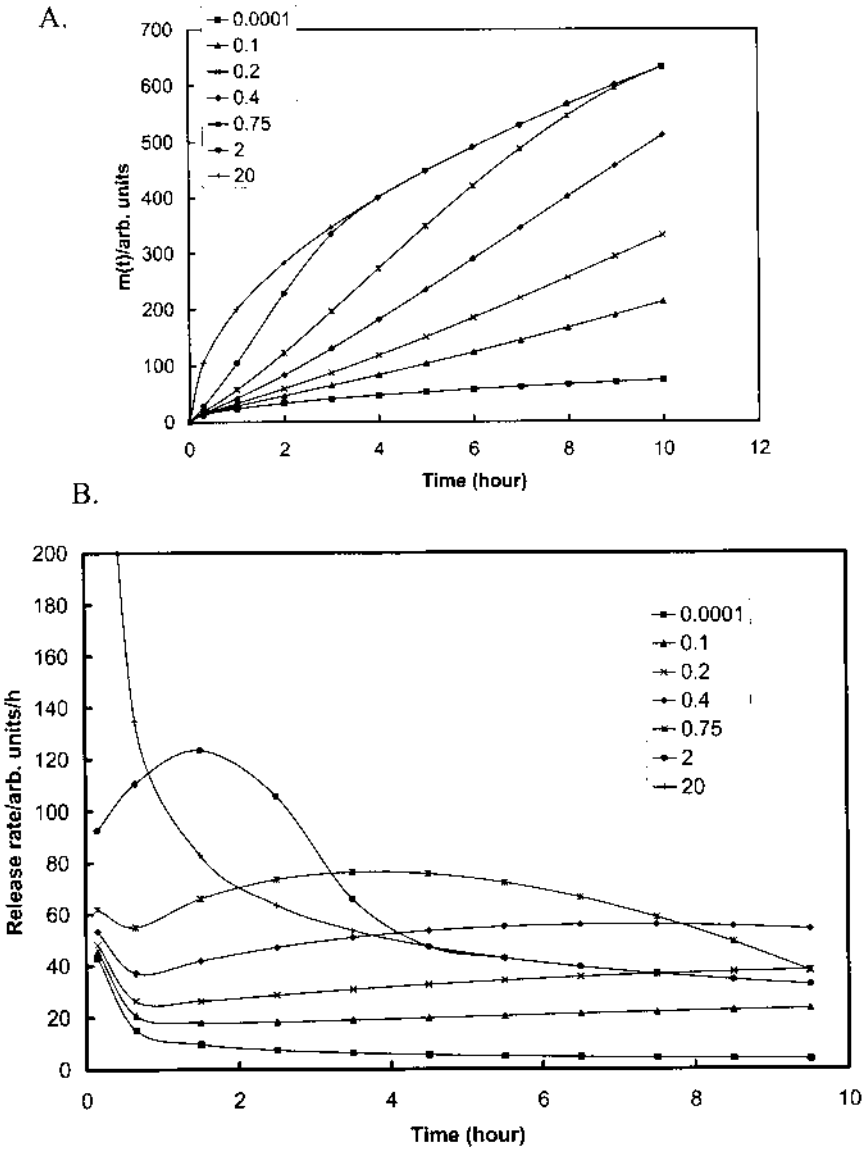


Figure 6 (A) Simulated release profiles of Smartrix tablets with different erosion rates. (B) Simulated release rates of Smartrix tablets with different erosion rates.

Copyright © 2003 Marcel Dekker, Inc.

with $m(t)$ being the amount of drug released at time t, and $A(t)$ being the "active" surface area of the core at time t, meaning the surface area that is available for drug release. The initially higher drug concentration under a newly uncovered part of the surface is not considered in this model. However, the error introduced by this simplification is small, because lateral diffusion compensates partly for that.

The "active" area $A(t)$ increases as the erosion process of the cover layers continues, thereby exposing new portions of the surface of the core layer. The creation of additional surface areas that becomes available for drug release occurs only at the top and bottom surfaces of the core. An additional "active" surface dA created by erosion is given by:

$$dA = \pi(2*r*dr - (dr)^2) \tag{5}$$

The erosion process is assumed to occur linearly with time as long as "sink" conditions are maintained for the erosion process. Under those conditions, a constant erosion rate k (mm/hour) can be assumed and thus:

$$dr = k\,dt \tag{6}$$

This equation is valid for linear surfaces (flat faced or conical). The effective surface area of conical-shaped cores is determined by multiplying the projection area with a geometry factor, which may be modeled numerically by adjusting k accordingly. Combination of Eqs. (5) and (6) gives:

$$dA = \pi*k*(2*r*t - k*t^2) \tag{7}$$

Equation (7) is valid for $k*t < r$. Upon completion of the erosion, the drug release follows again the $\sqrt{t}$ law [Eq. (1)]. The total active surface is given by:

$$A(t) = A_s + 2*\pi*k(2*r*t - k*t^2) \tag{8}$$

with A_s being the edge area of the tablet $A_s = h*2\,\pi*r$, which was not initially covered by the eroding layers. Equation (8) in Eq. (4) gives the final equation:

$$m(t) = Q(t)*A(t) = k_1*t^{0.5}*(A_s + 2*\pi*k(2*r*t - k*t^2)) \tag{9}$$

which is valid for $k*t < r$; and, upon completion of the erosion:

$$m(t) = k_1*t^{0.5}*(A_s + 2*\pi*r^2) \tag{10}$$

Equation (10) was used to simulate the effect of erosion on the drug release from matrix cores (Fig. 6A). The diameter of the tablet was 15 mm, the height of the core was 2 mm, the hybrid constant k_1, which defines the properties of the core, was set as 1. Thus the results are in arbitrary units. The erosion rate k was varied between 0.0001 and 20 mm/h, and the simulation was performed for a release period of 10 h. The case $k = 0.75$ represents the optimal scenario: the erosion takes 10 h to complete, meaning that the "geometric compensation" of the de-

Copyright © 2003 Marcel Dekker, Inc.

crease in drug release occurs throughout the entire release period. Smaller k values mean that the erosion process is not completed at the end of the intended release period, which results in an incomplete drug release. This is demonstrated in Figure 6A. All profiles that were generated using erosion times that matched or were close to the intended release period are sufficiently linear. It is demonstrated that the release properties can be easily scaled. Figure 6B shows the first derivatives of the profiles from Figure 6A, which represent the corresponding release rates. The release rate is very sensitive to deviations from linearity. It is demonstrated that the release rate for small values of k is nearly constant except for the first point, indicating that an initial burst dose is released from the edge of the tablet. Eventually, the combination of depletion of the outer zones and the "geometric compensation" results in constant release rates. Between $k = 0.4$ and 0.75, the release rates are acceptable for the duration of the application. If the erosion of the cover layers occurs too fast, the release profiles become biphasic as can be seen from the increasing curvature of the release rates and the profiles.

While it can be demonstrated that the decrease in drug release from a matrix can be compensated by an erosion-controlled surface increase, it should be noted that the model proposed here is only of limited use as a tool in product development. The assumptions and simplifications used in this approach limit its applicablility for practical development purposes. It is, however, useful for understanding the possibilities and limitations of controlling the release of a drug from a matrix by controlled erosion.

B. Experimental Results

1. Formulation and Processing Aspects

a. Core Matrix Layer The release profile of a drug from Smartrix tablets is determined by the increase of release surface caused by erosion of the cover layers. To ensure good reproducibility of the release characteristics, two parameters need to be precisely controlled, the surface area of the matrix core and the rate of erosion of the cover layers. For the surface area of the core to remain unchanged over the duration of the application, the core must not undergo any swelling. Materials that produce such inert porous plastic matrices include polyvinyl chloride [20], vinyl acetate/vinyl chloride copolymer [21], and ethyl cellulose.

The release properties of the drug from the core depend on the ratio of soluble to insoluble components, their particle sizes, the level of compaction, and the remaining porosity of the system. In addition to the physicochemical properties of the powder materials, the homogeneity of the blend and the distribution of the binders within the mix are essential. Consequently, processing conditions

Copyright © 2003 Marcel Dekker, Inc.

selected for the granulation process determine the porosity of the granules and, eventually, the compression parameters of the final tablet. If the homogeneity of the wet mass is critical, high shear mixing is a preferred granulation method. However, depending on the properties of the drug, direct compression of the cores might be an option as well.

Throughout the process, the viscosity and the particle structure (consistency) of the blend are constantly monitored to determine the end-point of the granulation process. Monitoring these two parameters ensures good reproducibility of the properties of the granules. Figure 7 shows a typical wet granulation diagram. From Figure 7 it can be seen that both consistency and viscosity drop after the entire amount of granulation liquid has been added but eventually increase again, indicating that the distribution of the granulation liquid in the powder blend is not yet completed. The mixing continues until both parameters have reached their predetermined end-point [22].

b. Eroding Cover Layers The cover layers need to exhibit narrowly defined erosive properties, but at the same time maintain good bonding to the core. The erosion rate has to be adjusted to match the intended duration of drug release to provide the required continuous increase of surface area of the core over the duration of the application. Depending on the dosing interval, erosion times between 5 and 10 h and possibly more are required.

To ensure a tight bonding between the cover layer and the drug-containing matrix throughout the erosion process, swelling of the cover layer must be pre-

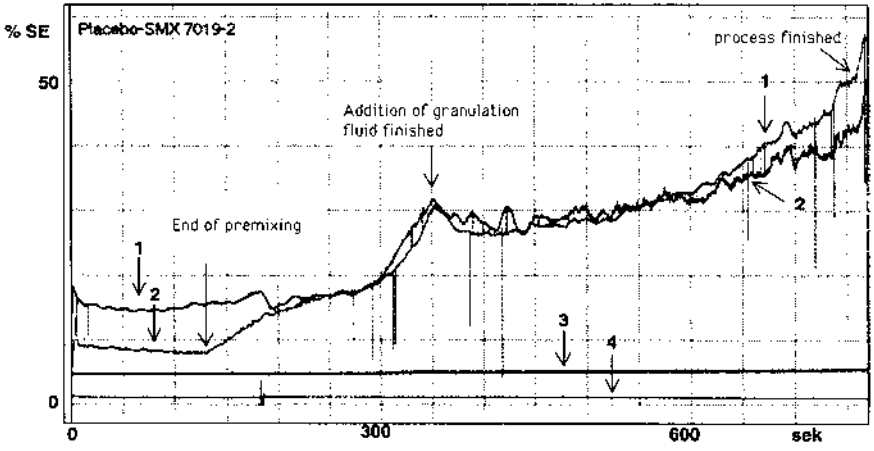


Figure 7 Wet granulation diagram. 1 = viscosity, 2 = consistency, 3 = mixer speed, 4 = chopper speed.

Copyright © 2003 Marcel Dekker, Inc.

vented, which limits the selection of materials that can be used for the eroding layer. Rather, the erosion has to be driven primarily by the dissolution of the components forming the eroding layer, and the total erosion time depends on the concentration of water-soluble components.

In practice, the problem is to find a cover layer formulation that shows a more or less constant erosion rate, does not swell (and thus compromise the layer bonding), and forms a strong bond with the core layer. This means that disintegration becomes an important factor to control the erosion process. Adding insoluble components to the formulation will extend the total erosion time. Ultimately, the erosion of the cover layers represents a complex process involving dissolution of water-soluble and disintegration of insoluble components. A critical parameter affecting the disintegration time is the particle size of the primary particles. It is essential to establish processing parameters for the wet granulation process that ensure a reproducible particle size of the granules.

Erosion may be studied using the USP XXIII disintegration apparatus [22]. Using cover plates results in a higher mechanical stress of the tablets. If the erosion is primarily driven by dissolution, mechanical stress of the tablets should have little effect on the resulting total erosion time, while in formulations with higher concentrations of insoluble components, the mechanical stress induced by the cover plates should affect the erosion process and the total erosion time should decrease. This is demonstrated in Figure 8. The concentration of insoluble formulation components increases from formulation 6070 to formulation 7018 (Fig. 8). As long as the erosion process is primarily driven by dissolution, mechanical

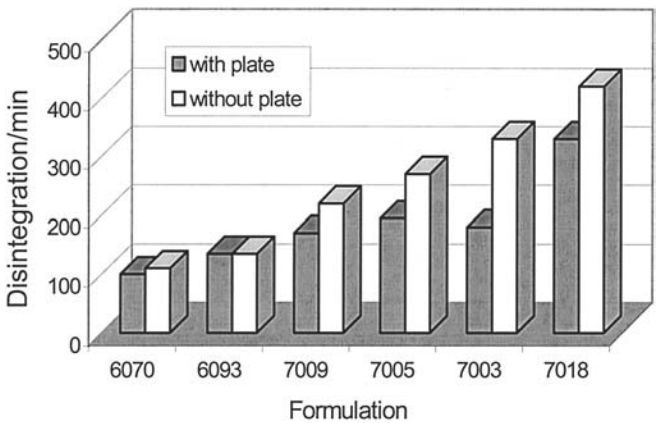


Figure 8 Relationship between total erosion time and concentration of insoluble components. (Modified after Dietrich [22].)

Copyright © 2003 Marcel Dekker, Inc.

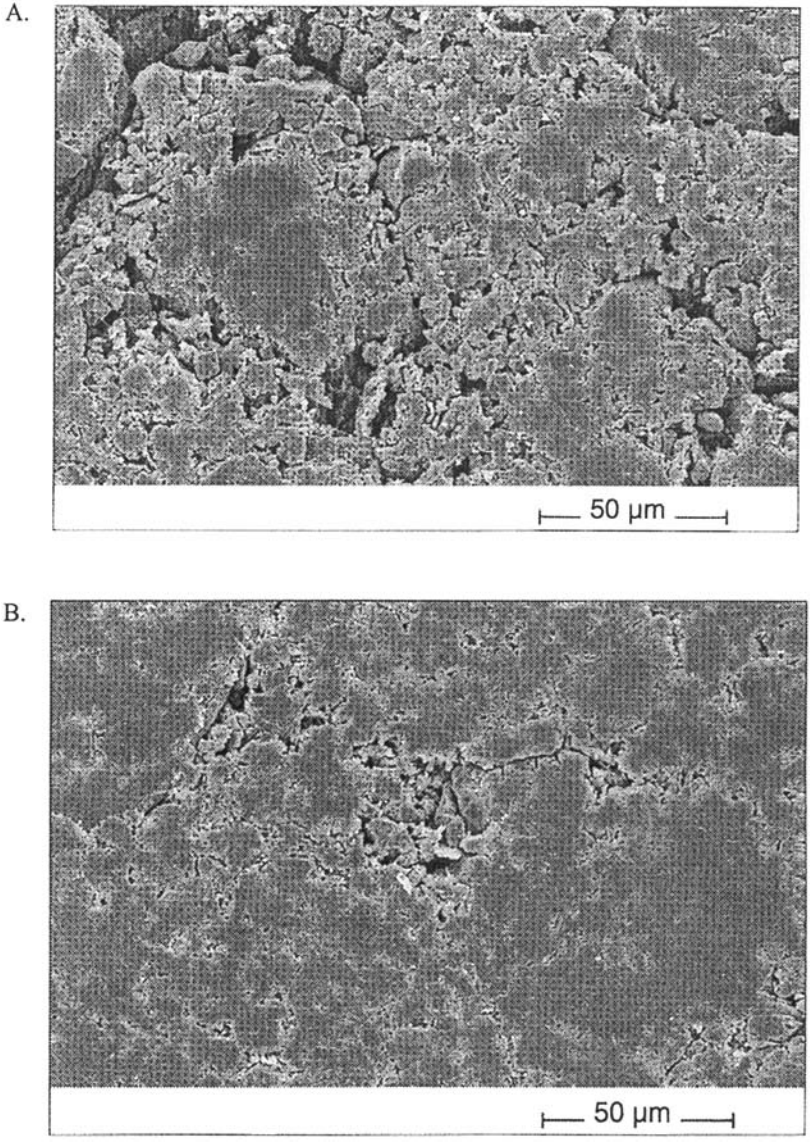


Figure 9 (A) REM scan of surface of core pressed at 5 kN (500×). (B) REM scan of surface of core pressed at 15 kN (500×).

Copyright © 2003 Marcel Dekker, Inc.

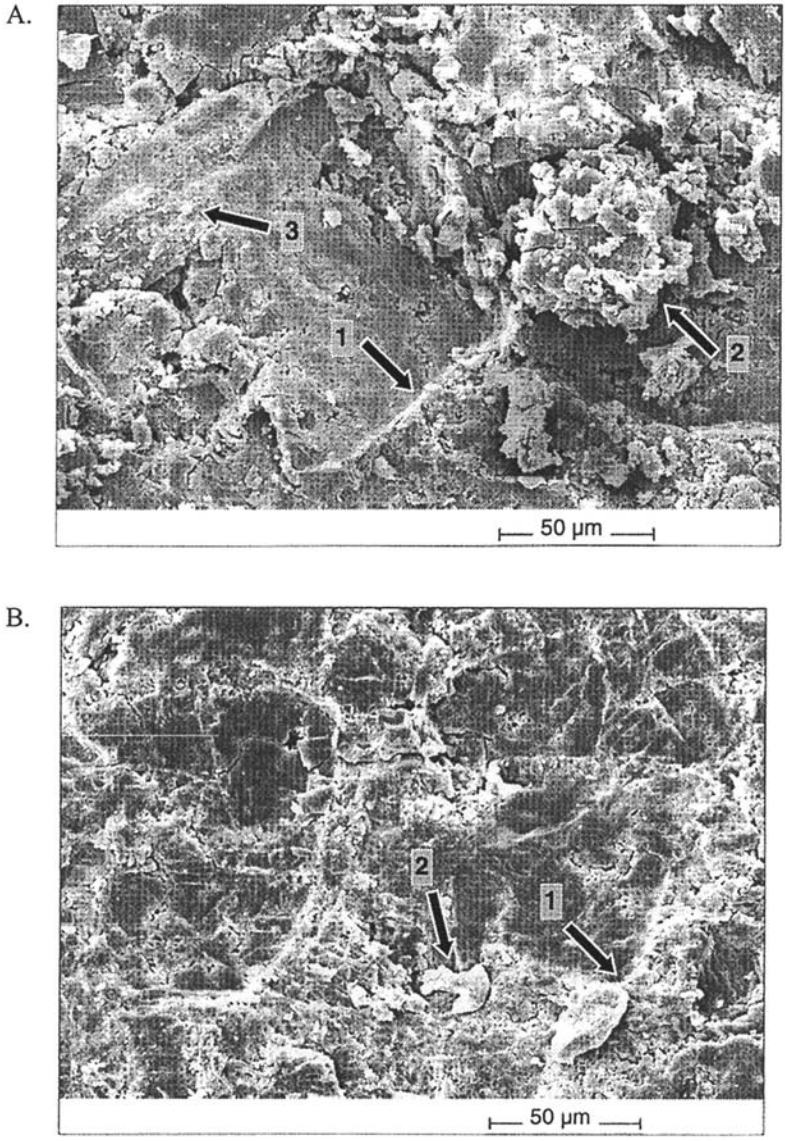
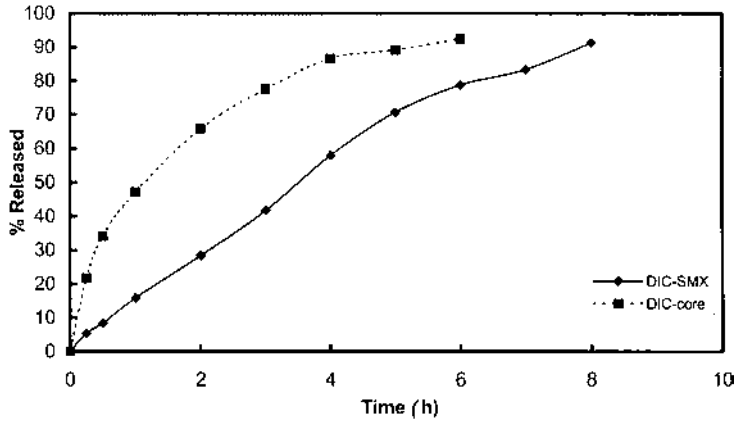
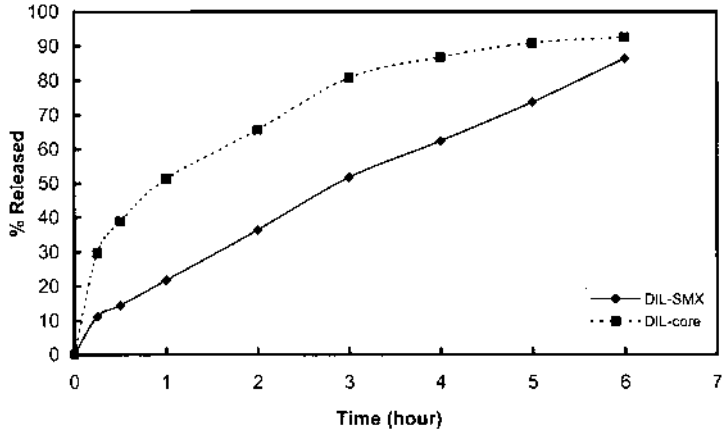


Figure 10 (A) REM scan of surface of core after final compression. Cores pressed at 5 kN (500×). (B) REM scan of surface of core after final compression. Cores pressed at 15 kN (500×).

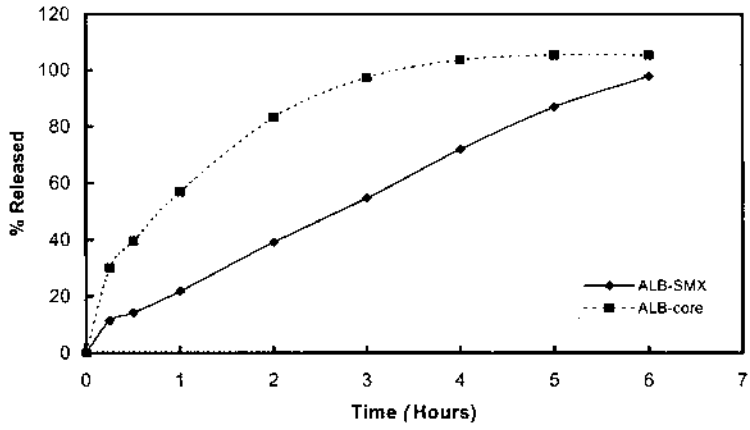
Copyright © 2003 Marcel Dekker, Inc.



(a)



(b)



(c)

Copyright © 2003 Marcel Dekker, Inc.

stress has only a small effect on the overall erosion time. As the concentration of insoluble components increases and the erosion process is more driven by disintegration, mechanical stress affects the overall erosion time.

2. Layer Building

A strong bond between cover layers and the core matrix layer is mandatory to ensure and erosion-controlled linear release of the drug from the core matrix. Obviously, the physicochemical properties of the formulations are important factors influencing the layer bonding as are the surface roughness and the hardness of the core and hence its susceptibility to further compression. In that respect, the precompression force is an essential parameter. If the compaction of the core granules exceeds a certain range, a tightly packed, "closed" surface of the core is formed and no penetration of particles of the cover layer into the core layer will occur during the main compression, which is essential for the formulation of a strong bond between the two layers. The results would be three separate layers with poor, if any, adhesion.

Dietrich studied the relationship between surface structure and layer bonding in complex multilayered tablets using laser profilometry and rapid-eye-movement imaging [22]. If the bonding between the two layers is mainly driven by adhesion, the resulting bond is weak and the layers will separate upon exposure to laminar shear force.

A sufficient anchorage of the cover layer on the matrix requires a partial penetration of particles of the cover layer into the matrix layer. The penetration depth depends on the surface structure and hardness of the matrix layer. Figure 9 illustrates the effect of the press force on the surface structure of matrix cores. At a press force of 5 kN, as shown in (A), a loose compaction of the primary particles takes place; deformation of the granules is minimal, and the structure of the agglomerates remains mostly intact. If the press force is increased to 15 kN, as shown in (B), the agglomerates are destroyed, and a tight network with an almost closed surface is formed. The hardness of the cores in (A) is 50 kN versus 179 kN in (B).

Figure 10 shows the effect of surface structure and hardness of the core tablet on the penetration depth. Image (A) shows deep indentations (1) in the

Figure 11 (a) Release profile of Diclofenac-Na from the core matrix (■) and from Smartrix tablets (◆). $r^2_{(\text{core matrix})} = 0.9897$; $r^2_{(\text{Smartrix})} = 0.9824$. (b) Release profile of Diltiazem from the core matrix (■) and from Smartrix tablets (◆). $r^2_{(\text{core matrix})} = 0.9832$; $r^2_{(\text{Smartrix})} = 0.9848$. (c) Release profile of Albuterol from the core matrix (■) and from Smartrix tablets (◆). $r^2_{(\text{core matrix})} = 0.9794$; $r^2_{(\text{Smartrix})} = 0.9947$.

Copyright © 2003 Marcel Dekker, Inc.

surface of a matrix layer that was produced at a compression force of 5 kN. The indentations were formed by crystals of the cover layer penetrating into the surface of the matrix layer. Particles of the cover layer may actually penetrate into the cover layer and bond permanently to the cover layer (2). Increasing the press force to 15 kN produces cores with a harder and denser surface (B). Indentation marks are also clearly visible but are much shallower. In this case, the particles of the cover layer (2) stay at the surface and no tight bond between cover layer and matrix is formed.

Shear forces required to cause layer separation after final compression of complex multilayered tablets were 98–237 N when using cores made with a press force of 5 kN, and 70 N when using cores pressed at 10 kN, respectively. No layer bonding could be achieved with cores that were pressed at a force of 15 kN.

3. In Vitro Dissolution

In vitro dissolution tests were performed to verify the concept of utilizing controlled erosion as a means of achieving zero-order drug release from matrix-based systems. Therefore, the dissolution tests were always performed using both finished Smartrix tablets and plain matrix cores. The physical characteristics of the matrix, particularly the hardness, can be expected to affect the release rate. Therefore, the press force applied to prepare the cores that were used in the dissolution study was increased from 5 kN to 15 kN and the resulting hardness values averaged 100 N.

The model compounds used for the dissolution studies were Diclofenac-Na, Diltiazem HCl, and Albuterol Sulfate. The dissolution tests were performed using the paddle method according to European Pharmacopoeia. Wire sinkers were attached to the tablets to keep them at the bottom of the dissolution vessel. Phosphate buffer pH 6.8 DAB 96 was used as an acceptor medium, and the concentrations of the active in the acceptor phase were determined spectrophotometrically. Figure 11a–c shows the dissolution profiles of the three compounds from plain matrices and Smartrix tablets. Each data point represents the average of $n = 3$ measurements. In the case of the plain matrices, cumulative amounts of drug released were plotted against $\sqrt{t}$. The data were then subjected to a linear regression analysis and r^2 was calculated to confirm the viability of the assumed model. In the case of the finished tablets, cumulative amounts released were plotted directly against t and r^2 was again determined from the linear regression analysis. The data confirm that, while the release from the plain matrix is sufficiently described by Higuchi's $\sqrt{t}$ law, a linearization of the profile can reliably be accomplished when increasing the release surface continuously by controlled erosion.

Copyright © 2003 Marcel Dekker, Inc.

IV. SUMMARY AND OUTLOOK

Smartrix tablets are complex multilayered tablets that consist of individually shaped layers, whereby the shape of the cover layers is determined by the shape of the core layer. The release of the drug from the core matrix layer(s) is controlled by erosion of the cover layers, which results in quasi-linear release profiles. To obtain the desired linearity of the release profiles, the rate of erosion of the cover layers has to be adjusted to match the intended release period. A strong bond between core matrix and cover layers is essential to ensure the desired release profile over the intended application period. A critical factor affecting the bonding strength is the surface structure of the core. The process for manufacturing Smartrix tablets requires a specially designed rotary press that is equipped with a transfer element for the precise positioning of the prepressed core in the die.

Complex multilayered tablets represent a viable alternative to existing single-unit oral controlled-release dosage forms. Attempts are being made to improve the cost-efficiency of the system by developing a limited number of "standard cover layers" with different erosion times that may be used as "off-the-shelf items" in the development of new drugs. The system is quite versatile and its unique design offers some new and exciting therapeutic options. Most importantly, it will be possible to combine two matrix layers that contain different active drugs and design the release profile of each drug to maximize its therapeutic effect.

REFERENCES

1. E Nelson. Pharmaceuticals for prolonged action. Clin Pharmacol Ther 4:283, 1963.
2. K Münzel, Der Einfluss der Formgebung auf die Wirkung eines Arzneimittels (The Effect of the Shape of a Dosage Form on its Efficacy). Basel: Birkhäuser Verlag, 1966, p. 290.
3. H Bechgaard. Critical factors influencing gastrointestinal absorption—what is the role of pellets? Acta Pharm Technol 28:149, 1982.
4. SS Davis. The design and evaluation of controlled release systems for the gastrointestinal tract. J Control Rel 12:27, 1985.
5. JN McMullen. Controlled release tablet. US patent 4,816,262, 1989.
6. MA Bayomi. Geometric approach for zero-order release of drugs dispersed in an inert matrix. Pharm Res 11:914–916, 1994.
7. BC Lippold. Slow and extended release products: mechanisms of release and possibilities of control. In: Blume, Gundert-Remy, Mölle, eds. Controlled/Modified Release Products. Stuttgart: Wissensch Verlagsgesellschaft mbH, 1991, pp. 15–34.
8. U Conte, L Maggi. Modulation of the dissolution profiles from Geomatrix multilayer tablets containing drugs of different solubility. Biomaterials 17:889–896, 1996.

Copyright © 2003 Marcel Dekker, Inc.

9. Y Qiu, N Chidambaram, K Flood. Design and evaluation of layered diffusional matrices for zero-order sustained release. J Control Rel 51:123–130, 1998.
10. L Yang, R Fassihi. Examination of drug solubility, polymer types, hydrodynamics and loading dose on drug release behaviour from triple-layer asymmetric configuration delivery devices. Int J Pharm 155:219–229, 1997.
11. MA Abraham, A Shirwaikar. Formulation of multilayered sustained release tablets using insoluble matrix system. Indian J Pharm Sci 59:312–315, 1997.
12. A Nangia, T Molloy, BJ Fahie, SK Chopra. Novel regulated release system based on geometric configuration. Proc Int Control Rel Bioact Mater 22:294–295, 1995.
13. N Chidambaram, W Porter, K Flood, Y Qiu. Formulation and characterization of new layered diffusional matrices for zero-order sustained release. J Control Rel 52: 149–158, 1995.
14. K Cremer, B Asmussen. Novel controlled release tablet with erodible layers. Proc Int Symp Control Rel Bioact Mater 22:732–733, 1995.
15. K Cremer. Verfahren zur herstellung von vorrichtungen zur kontrollierten freisetzung von wirkstoffen. German patent DE 44 16 926, 1995.
16. K Cremer. Vorrichtung zur kontrollierten freisetzung von wirkstoffen sowie ihre verwendung. German patent DE 43 41 442, 1998.
17. W Korsch. Mantelkernpresse. German patent DE 3 819 821, 1990.
18. W Korsch, M Schmett. Presse zur Herstellung ummantelter Tabletten. German patent DE 4 025 484, 1990.
19. T Higuchi. Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 52:1145–1149, 1963.
20. MS Vora, AJ Zimmer, VP Maney. Sustained release aspririn tablets using an insoluble matrix. J Pharm Sci 53:487, 1964.
21. RC Rowe. Sustained release plastic matrix tablets. Manuf Chem Aerosol News 3: 23–56, 1975.
22. P Dietrich. Schichthaftung in Komplex-Mehrschichttabletten. Ph.D. dissertation, Alber-Ludwigs-Universität, Freiburg I. Breisgau, Germany, 1999.

Copyright © 2003 Marcel Dekker, Inc.

7
TheriForm Technology

Charles W. Rowe, Chen-Chao Wang, and Donald C. Monkhouse
Therics, Inc., Princeton, New Jersey, U.S.A.

I. INTRODUCTION

TheriForm™ manfacturing of drug delivery devices is a novel method of fabrication based on Three Dimensional Printing™ (3DP™), a solid freeform fabrication technology. Dosage forms are fabricated in a layer-by-layer fashion using ink-jet printing technology to allow fine spatial placement of specific substances within the body of the dosage form, thus providing control over the release of active drug from the assembled structure.

This chapter will describe the TheriForm technology and its application to drug delivery systems, specifically oral controlled-release forms. It will also present the results of several studies with model active drugs to produce a variety of release profiles. Finally, the chapter will discuss the issues encountered during commercialization of the process.

The TheriForm process is a licensed application of the original 3DP patent [1] issued to Massachusetts Institute of Technology in 1993. The license issued to Therics, Inc. (Princeton, NJ) in 1994 covers the use of 3DP for manufacturing medical products including drug delivery devices. Additional patent filings by Therics, Inc. for specific applications of TheriForm have been completed, with more extensive disclosures expected as the process is expanded into new areas.

II. DESCRIPTION OF THE TECHNOLOGY

TheriForm technology has been previously described in the literature as a rapid prototyping method [2] and a pharmaceutical manufacturing process [3,4]. Fig-

Copyright © 2003 Marcel Dekker, Inc.

ure 1 is a diagrammatic representation of the TheriForm process. The process consists of a motion-controlled printhead that dispenses liquid into a thin powder layer. Each layer printed is a two-dimensional slice of the dosage form being manufactured. The powder bed is lowered after each printing pass, additional powder is spread, and the printing process is repeated with a new two-dimensional slice until the dosage form is completely built. The process allows placement of one or more active substances within selected locations inside the dosage form, along with other pharmaceutical materials that control the release properties of these actives. TheriForm can use this ability to construct dosage forms with unique and complex profiles that closely match ideal dosing schedules.

Previous publications have shown that TheriForm is capable of high accuracy placement of liquid droplets [5], high accuracy metering of active dosage [6], and the ability to contruct oral dosage forms with complex release profiles [3,4]. These complex release profiles are generally achieved by placing the active substance within various matrices to control the release of the active. These matrices are often compartments within the dosage form, surrounded by walls of the release-controlling material. The compartments can be made quite small, on the order of 500 μ to several millimeters.

TheriForm is based upon 3DP, a fabrication technique that has proven its versatility by being able to process many types of powders including metals, ceramics, polymers, and hydrogels. It is particularly useful for constructing parts in applications where control over microstructure and where internal device features are required, as in degradable tissue engineering matrices or drug delivery systems [7]. It is possible to microengineer the release characteristics of a delivery device and precisely control drug dosage. The computer-controlled axis and nozzle system delivers an accurate amount of drug to the interior of the construct where it has no contact with the friable exterior. Dosage forms built in this manner can be very complex in interior design, with the capablility of releasing multiple compounds in a controlled fashion through carefully designed placebo walls and barriers. TheriForm is also an economically competitive fabrication process. It is readily scalable and rapid formulation and reformulation is possible within the CAD file.

Controlled release of delivery devices fabricated using 3DP technology was initially demonstrated by Wu et al. at the Massachusetts Institute of Technology [8]. The devices resembled small checkerboards, and were composed of soluble polyethylene oxide walls and insoluble polycaprolactone floors and lids. Dyes were deposited in individual reservoirs, and their release was monitored, showing a two-dimensional erosion mechanism. Wu et al. concluded that the dye release was representative of the thickness and density of the reservoir walls as specified by the printing parameters.

Copyright © 2003 Marcel Dekker, Inc.

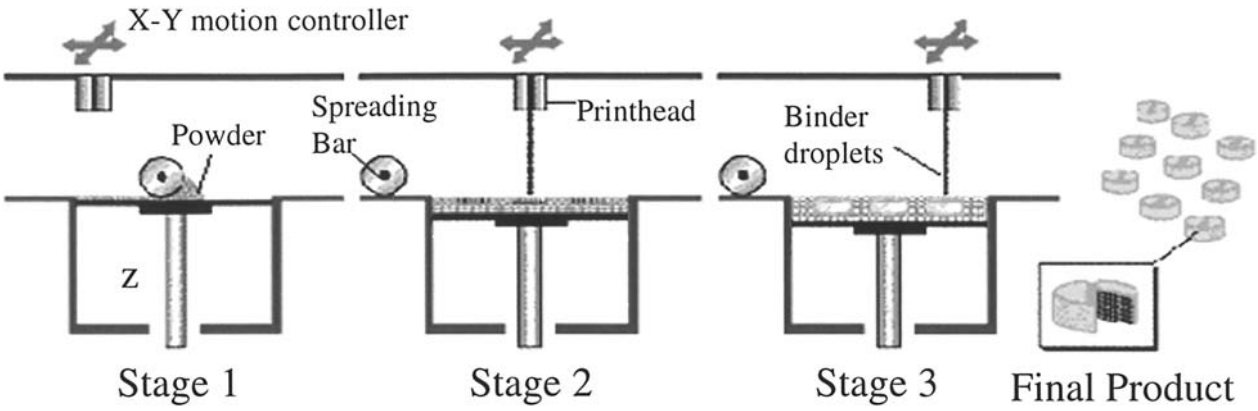


Figure 1 Schematic TheriForm process. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

III. RESEARCH AND DEVELOPMENT

Oral dosage forms were fabricated with a binder solution containing Eudragit® RL PO and a standard pharmaceutical grade microcrystalline cellulose powder (Avicel® PH 301, FMC). Eudragit RL PO is classified as an ammonio-methacrylic acid copolymer type B (USP/NF), and has an average molecular weight of 150,000. It is expandable and permeable and its properties are independent of pH [9]. A 20% (w/w) Eudragit RL PO/acetone solution was printed through a 45-μm nozzle with a flow rate of 0.85 g/min. A total of 20 layers of 200 μm each was used in oral dosage form construction. The printhead velocity was 140 cm/s. Three rows of devices were printed with line spacings of 70, 100, and 130 μm to produce devices with polymer volume fractions of 16.7%, 11.7%, and 9%, respectively.

Six placebo layers were printed using the polymeric binder to form the floor of the oral dosage form. Next, eight active-containing layers were printed, followed by another six placebo layers to form the top cap of the dosage form. The drug was incorporated in the active-containing region using the following two-step procedure. The first step was to print a binder identical to the placebo layers. Next, a total of 4.23 μL of 30% (w/w) chlorpheniramine maleate solution was deposited in three passes of the printhead. The powder bed was dried between each pass to minimize bleeding due to oversaturation with the binder liquid. The piston was lowered, and the process was repeated for eight layers to deliver a total dosage of 5.45 mg into the region. It was assumed that migration and capillary effects were small and that the drug distribution was uniform.

Figure 2 shows the release profile of the oral dosage forms in simulated intestinal fluid. Note that by varying a single operating parameter (line spacing in this case), it is possible to alter the release rate of the oral dosage forms. Using these techniques, it is possible to use TheriForm manufacturing to rapidly prototype an oral dosage form formulation. Furthermore, all three of these formulations can be manufactured in a singular print run.

One of the significant advantages of TheriForm technology is its flexibility in constructing different structural designs. This allows for modification of drug release from $t^{1/2}$ kinetics, usually obtained from a monolithic oral dosage form, to different release kinetics to meet therapeutic needs. For example, surrounding a monolithic drug-containing matrix with a drug-free polymeric shell may result in a near-zero-order release by retardation of the initial release rate, as demonstrated by the release profiles for isosorbide-5-mononitrate (ISMN) dosage forms in Figure 3. The binder and powder formulations used to fabricate this dosage form are displayed in Table 1.

The drug release rate of such a core-shell design can be adjusted by the architecture and structure of the core and/or the shell region. Fabrication parameters such as flow rate, drop-drop spacing, line-line spacing, and powder layer

Copyright © 2003 Marcel Dekker, Inc.

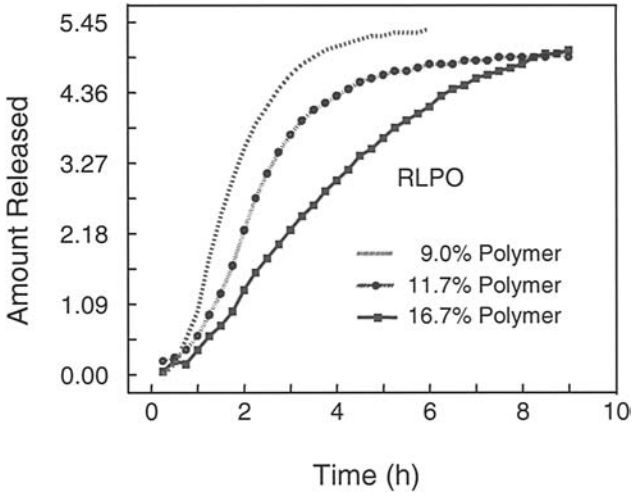


Figure 2 Dissolution profiles for chlorpheniramine maleate oral dosage forms fabricated using Eudragit RS PO as release-controlling polymer. (See color insert.)

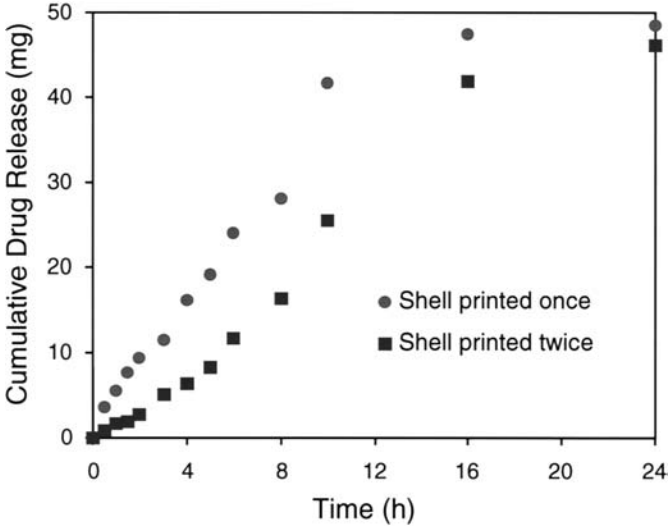


Figure 3 Dissolution profiles for isosorbide-5-mononitrate dosage forms printed with different amount of shell binder solution. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Compositions of Binder and Powder Formulations for ISMN Controlled-Release Oral Dosage Form (ratio and percentage by weight)

Drug binder	40% ISMN in ethanol-water (70:30), 0.3% FD&C Yellow #6
Shell binder	5% Eudragit L-100 in ethanol-water (50:50) solution
Powder	30% Avicel PH 301, 50% Eudragit L-100, 13.5% spray-dried lactose, 5% tricalcium phosphate, 1.5% Cab-O-Sil

thickness can be varied to change the amount of binder solution deposited onto the powder bed, and consequently influence the polymer content and the density of the selected region. For example, the release rate was further decreased when the shell region was printed twice with the shell binder solution (Fig. 3). The change in release rate was due to more polymer and solvent delivered to the shell region, which resulted in a denser matrix through stronger binding and fusion of the powder particles. In addition to variation of the density of the matrix, the drug release rate for the core-shell delivery system may be manipulated by (a) variation of shell thickness, (b) variation of polymer types and concentrations in shell binder solution, and (c) addition of placticizers to the binder solution or addition of excipients to the powder bed composition.

The core-shell concept has also been applied to the fabrication of dosage forms containing toxic compounds. A delivery system with shell-core structure (Fig. 4) was designed to avoid unnecessary contact with toxic compounds by

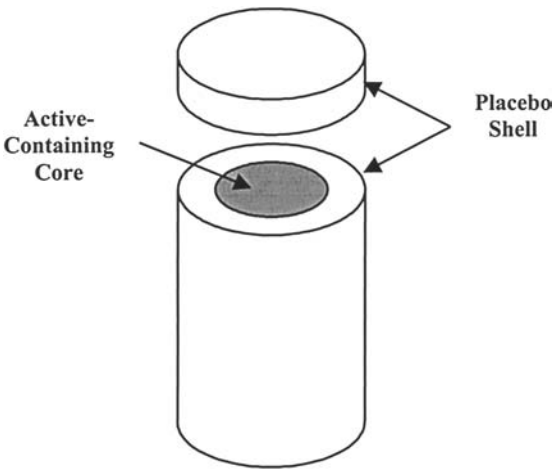


Figure 4 Schematic of design of Therics' 9-nitrocamptothecin core-shell dosage forms.

Copyright © 2003 Marcel Dekker, Inc.

manufacturing and health professionals. In this study, a suspension containing 2.5% (w/w) microfine 9-nitrocamptothecin, an anticancer compound, was formulated to deliver the active to the core of cylindrical constructs with a size designed for insertion into #3 capsule shells. The shell region functioned as a release barrier to retard the initial burst of active, which has been observed with the traditionally formulated capsules (Fig. 5), in an attempt to minimize gastrointestinal side effects. The powder mixture was composed of 49% (w/w) hydroxypropylmethyl cellulose (Pharmcoat 603, Shin-Etsu Chemical Co.), 49% spray dried lactose (Pharmatose® DCL 11), and 2% Avicel® PH 301. The shell binder was 11% (w/w) aqueous PVP K25 solution.

By confining the active to the suspension binder, the concern with exposure to airborne drug particles from powder mixing processes can also be eliminated. The release-controlling property of the shell matrix can be adjusted by variation of fabrication parameters alone or in combination with other approaches previously described with the ISMN delivery system.

An example of a more complex release profile is a dual pulsatory device. These dosage forms were designed to release the initial burst first in the stomach at low pH and pulse the second payload in the intestine at high pH. This was accomplished by printing drug compartments inside different polymer environments. One drug compartment was printed into a polymeric section of cationic

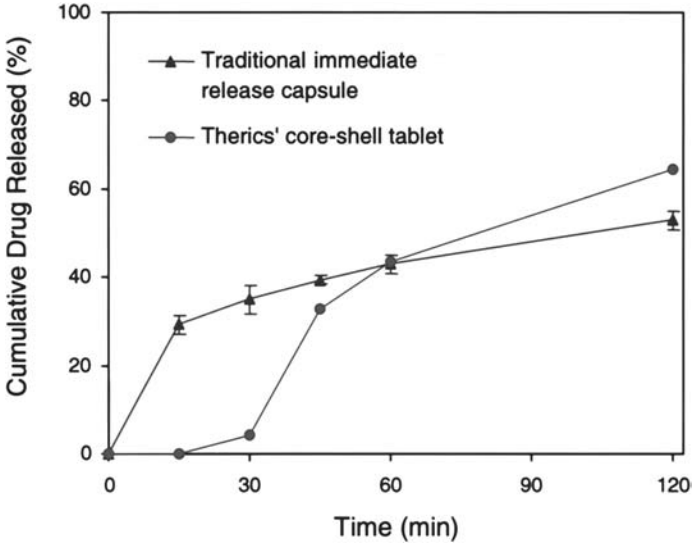


Figure 5 Dissolution profiles for Therics' 9-nitrocamptothecin core-shell dosage forms and traditional capsules. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

nature (Eudragit E-100) and another drug compartment was printed into a polymeric section of anionic nature (Eudragit L-100). These dosage forms were manufactured with a 25-gm dose of diclofenac sodium. A schematic of the device is shown in Figure 6.

The powder used for these devices was 30 wt% Avicel PH301, 30 wt% spray-dried lactose (Pharmatose DCL 11), and 40 wt% Eudragit L100. The L-100 binder was 5% (w/w) Eudragit L100 in ethanol. The printing parameters were 200-μm layer thickness, 100-μm line spacing, 105-cm/s printhead velocity, and a 1.1-g/min flow rate. The E-100 sections of the device were printed with a solution of 13.5% (w/w) Eudragit E-100 in acetone. The printing parameters were 200-μm layer thickness, 100-μm line spacing, 105-cm/s printhead velocity, and a 1.28-g/min flow rate.

Two E-100 placebo layers were printed, followed by three drug-containing layers and two additional E-100 placebo layers to complete the first compartment. The second compartment was six placebo L-100 layers, six active-containing layers, and six placebo L-100 layers. The top compartment was built identically to the first compartment. The dissolution profiles of the dual pulsatory delivery systems are demonstrated in Figure 6. The dissolution testing was performed using simulated gastric fluid at pH 2 for 1 h, then changing the solution to simulated intestinal fluid at pH 7.4.

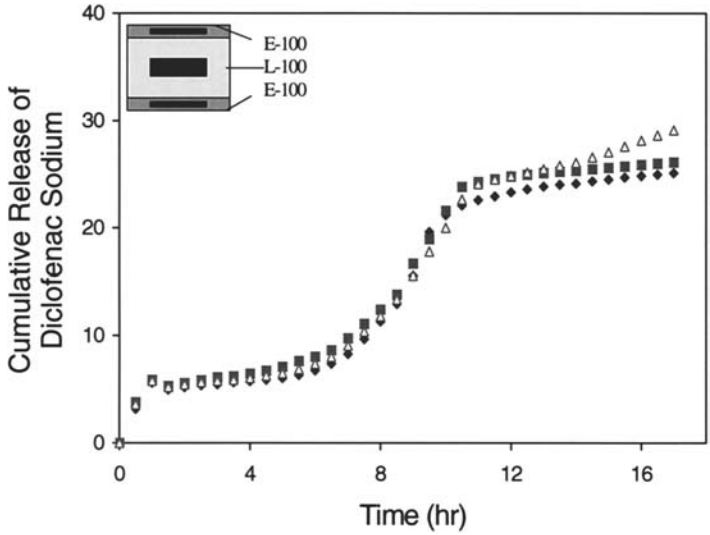


Figure 6 Schematic of structure and dissolution profiles for pulsatile-release diclofenac sodium oral dosage forms. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

IV. REGULATORY ISSUES

Although TheriForm technology differs from traditional granulation and tabletting in the mechanism of fabrication of dosage forms, regulatory issues associated with mixing of pharmaceutical solids and preparations of granulation liquids can be directly applied to prefabrication TheriForm processes. Likewise, postfabrication regulatory issues for TheriForm technology such as drying, dedusting, and packaging are similar to other pharmaceutical technologies for oral dosage forms. Cleaning is facilitated by modular construction, allowing for easy changeover of powder beds, and rapid plug-in printhead assemblies. Computer software validation is also standard.

The major difference from traditional technology lies in equipment validation, i.e., equipment installation, equipment operation, and equipment use in processing. Since TheriForm machines are designed with validation in mind, however, such processes can be pursued without significant difficulty. Furthermore, with electronic monitoring systems for liquid delivery on TheriForm machines, droplets and flow rate monitoring ensure accurate drug loading and material delivered to the dosage forms. Real-time characterization can provide much more reliable information than the "end-point monitoring" commonly employed for traditional pharmaceutical processes such as granulation and tabletting. Precision and accuracy of printhead performance is also enhanced by close control of humidity and temperature of the environment.

V. TECHNOLOGY POSITION/COMPETITIVE ADVANTAGE

With the flexibility in fabrication of delivery systems (because of precise geometric positioning of active and preprogrammed microarchitecture and macrostructure), TheriForm technology can be applied to design and develop products that are simply too complex for traditional manufacturing processes, or that require a level of precision that cannot be achieved with other technologies. Common applications of TheriForm technology for pharmaceutical delivery systems include, but are not limited to, the following fields:

1. Microdose, for potent compounds with narrow therapeutic windows, which require small-dose delivery with precise drug loading. By delivering the active to the dosage forms in the liquid state, the variation in drug content uniformity normally encountered with conventional dry powder mixing or wet granulation can be effectively minimized. A placebo outer shell can be fabricated to avoid unnecessary physical or human contact as well.

Copyright © 2003 Marcel Dekker, Inc.

2. Pulsatile release, for actives that need to be given to patients at inconvenient administration schedules for the desired therapeutic effect. For example, a dosage form can be designed to release an anti-Parkinson's compound at midnight to achieve the therapeutic blood level to control the patient's morning symptoms. The core-shell design can be applied to generate a lag phase and an immediate drug release phase for such a therapeutic/chronobiological purpose.
3. Zero-order release or release kinetics following specific pharmacokinetic/pharmacodynamic models. Several technologies have been used to fabricate dosage forms with zero-order release; however, most of them require multiprocesses during their manufacture. With TheriForm technology, fabrication can be achieved within one single process. Furthermore, with the flexibility of the TheriForm process, the release pattern can be adjusted to match specific pharmacokinetic/pharmacodynamic needs. For example, the dosage form may include drug gradients emanating from the peripheral to the central region to allow the drug release rate to increase with time. The unique release kinetics can be used for certain actives that cause tolerance due to loss of receptor sensitivity.

VI. FUTURE DIRECTIONS

Applications of the TheriForm technology continue to be extensively explored at Therics. The following fields provide potential new directions for future development of the technology:

1. Delivery of macromolecules such as protein and peptides. The technology can also be extended to localized biopharmaceutical delivery of gene fragments to a wound site.
2. Implantable delivery systems for hormone replacement therapy, drug addiction treatment, and other long-term therapeutic systems. Data obtained from an implantable delivery system containing ethinyl estradiol have demonstrated excellent in vivo–in vitro correlation [10]. Therics will focus on biodegradable systems that eliminate the need of postdosing surgical removal to significantly enhance patient compliance, as well as local delivery of antibiotics and pain medication to the wound site following surgery.
3. Tissue repair scaffold products, with or without therapeutically active ingredients. With the capability of including carefully designed microarchitectural features, TheriForm technology is superior to other existing tissue scaffold fabrication technologies by providing pores and

Copyright © 2003 Marcel Dekker, Inc.

channels for guided ingrowth, proliferation, and differentiation of tissue cells. Growth hormones or bone morphogenetic proteins can be included in such products to further accelerate the healing process.

REFERENCES

1. MJ Cima, JS Haggerty, EM Sachs, PA Williams. Three-dimensional printing techniques. US patent 5,204,055, 1993.
2. EM Sachs, MJ Cima, P Williams, D Brancazio, J Cornie. Three-dimensional printing: Rapid tooling and prototypes directly from a CAD model. J Eng Ind 114:481–488, 1992.
3. WE Katstra, RD Palazzolo, CW Rowe, B Giritlioglu, P Teung, MJ Cima. Oral dosage forms fabricated by Three Dimensional Printing. J Control Rel 66:1–9, 2000.
4. CW Rowe, WE Katstra, RD Palazzolo, B Giritlioglu, P Teung, MJ Cima. Multimechanism oral dosage forms fabricated by Three Dimensional Printing. J Control Rel 66:11–17, 2000.
5. WE Katstra, CW Rowe, MJ Cima. Controlling drug placement during the fabrication of complex release oral dosage forms by 3DP. Proc Int Symp Control Rel Bioact Mater 27:413–414, 2000.
6. J Yoo, E Bornancini, A Yang, G Shanahan, D Monkhouse. Content uniformity study of microdose tablets fabricated by the TheriForm process. Annual meeting of the American Association of Pharmaceutical Scientists, Boston, Nov 2–6, 1997.
7. LG Cima, JP Vacanti, CA Vacanti, D Ingber, D Mooney, R Langer. Tissue engineering by cell transplantation using biodegradable polymer substrates. J Biomech Eng 113:143–151, 1991.
8. BM Wu, SW Borland, RA Giordano, LG Cima, EM Sachs, MJ Cima, Solid free-form fabrication of drug delivery devices. J Control Rel 40:77–87, 1996.
9. Pharma Eugragit Polymers Product Range Information Booklet, Creanova Inc, Somerset, NJ.
10. S Kumar, AP Sayani, MJ Cima, MM Mason, TG West, AY Yang, DC Monkhouse. In vivo/in vitro correlation of ethinyl estradiol release from biodegradable implants fabricated by the Theriform process. Annual meeting of the American Association of Pharmaceutical Scientists, New Orleans, LA, Nov 14–18, 1999.

Copyright © 2003 Marcel Dekker, Inc.

8

Accudep™ Technology for Oral Modified Drug Release

David R. Friend, S. S. Chrai,* G. Kupperblatt,† and R. Murari
Delsys Pharmaceutical, A Division of Elan Operations, Inc., Monmouth Junction, New Jersey, U.S.A.

Jackie Butler, T. Francis, Araz A. Raoof, and Brian McKenna
Elan Drug Delivery, Athlone, Ireland

I. INTRODUCTION

The Accudep™ technology has been developed to address several issues in the design and manufacture of a range of dosage forms, including those for oral administration. This technology is being applied to a range of product areas including immediate-release dosage forms, super generic products, and novel controlled-release formulations. This chapter describes the recent advances made using the Accudep process to create the latter, namely controlled-release dosage forms. Specifically, this chapter covers (a) the Accudep process, (b) its application to the creation of oral modified-release (controlled-release) dosage forms, and (c) data collected from in vitro and in vivo studies.

II. HISTORICAL DEVELOPMENT

Delsys Pharmaceutical has been studying the application of dry powder deposition (Accudep) technology in the development of oral modified-release (controlled-release) products. The goal of this program is to identify highly flexible delivery designs that will accommodate many drugs of diverse physicochemical

* *Current affiliation*: Chrai Associates, Cranbury, New Jersey, U.S.A.
† *Current affiliation*: The Dow Chemical Company, Midland, Michigan, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

characteristics and dose ranges, and facilitate engineering of immediate as well as controlled release of the pharmaceutical active powder.

The system design differs from currently marketed controlled-release products in that it avoids the conventional pharmaceutical processes such as mixing, blending granulation, drying, sizing, and compression. Instead, the proposed system utilizes active drug moieties as pure active ingredient, and achieves controlled release through the use of polymeric films of various release characteristics.

The basic principle of electrostatic deposition is well known from classic physics—opposite charges attract. In his early electrical experiments in the eighteenth century, Coulomb measured the magnitude of the electrostatic force and proposed a formula that governs it. Coulomb's law states that two charges separated by a distance exert a force on each other that is directly proportional to the product of their charges and inversely proportional to the square of their distance (similar to Newton's gravitational law). This force is attracting or repelling for opposite or similar charges, respectively.

The most common example of electrostatic deposition is the copying machine that performs precise deposition of ink particles. Xerography (i.e., electrophotography) is the largest and most recognized industry that utilizes the principles of electrostatic science for printing and copying. It utilizes "dry ink" (toner) for printing on a designated area of the paper. Toner particles are charged, conveyed, transferred, and then fused to the paper, thereby creating the print or copies that are familiar to everyone.

In the Accudep process, pharmaceutical powders acting as toner are charged, then transported to a chamber wherein dispersion and deposition take place [1]. Deposition of material is accomplished by establishing a pattern of charges of one polarity on a substrate where deposition is desired, and delivering a supply of the material to be deposited in the form of small, oppositely charged particles. The attractive Coulomb force created within the system accelerates and focuses the particles toward the desired regions of the substrate. In practice, the deposition process is more complex because typical charged patterns on the substrate produce nonuniform electric fields, particularly at edges. The electric field created by the applied potential to the substrate changes continuously as charged powder deposits on the substrate. This interaction between powder and substrate provides an additional control mechanism for dosage size control. The momentum of the charged particles must also be accounted for to accurately determine where the particles will be deposited. Accurately addressing these variable factors with feedback control sensors enables a quantitative model for designing and controlling automated systems for the deposition of materials by electrostatic deposition. The current Accudep process used by Delsys is shown in Figure 1.

For the purpose of controlled release, Accudep cores, prepared using the Accudep process, are alternately placed between polymeric films acting as ero-

Copyright © 2003 Marcel Dekker, Inc.

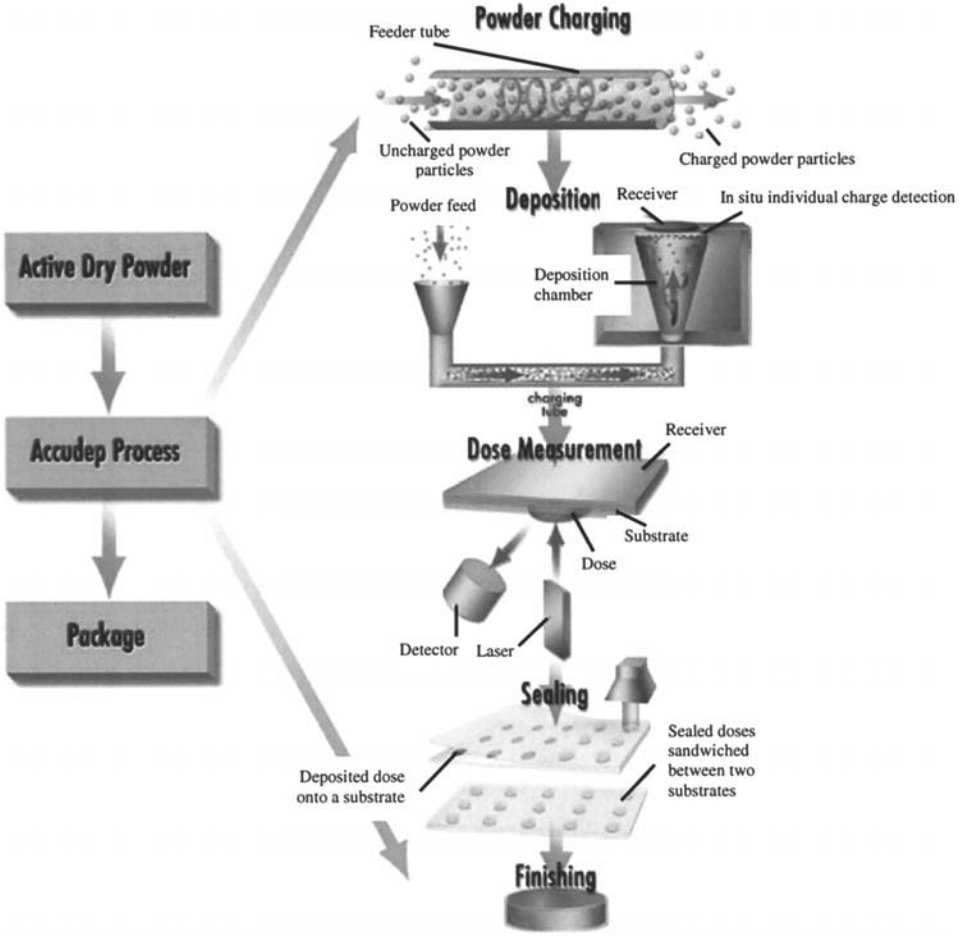


Figure 1 The Accudep process. Following powder charging, the drug powder is deposited onto a suitable polymer film. The resulting pattern of drug deposits is sealed and punched out to obtain discrete dose units. The units can be processed in a variety of ways, including the creation of novel controlled-release dosage forms. (See color insert.)

sional barriers. The number of cores as well as the amount of drug per core can be varied to achieve a desirable sustained or pulsatile release profile. It addition, two drugs can be codelivered from the same delivery system. It is also feasible to control release rate by varying the number of polymeric film layers, their composition, and their thickness. Furthermore, this delivery system is typically coated with an impermeable coating on the sides to constrain drug release. This design

Copyright © 2003 Marcel Dekker, Inc.

provides yet another design variable: keeping either one or both ends open (i.e., without impermeable coating). This design variable permits one to engineer an immediate release component of the release profiles as well as providing an additional means for modulating the controlled-release portion of the drug. The finished dosage form is intended to be elegant, easily swallowable, and economical to manufacture.

III. DESCRIPTION OF TECHNOLOGY

The Accudep technology is currently used to prepare oral dose units, called Accudep cores. The controlled-release systems under development are comprised of Accudep cores separated by erosional polymer films. Figure 2 illustrates such a system. The example in this figure consists of six layers, each of which contains three components. In each layer, an Accudep core is contained by a polymer ring. The layers are separated by rate-controlling polymer films. An impermeable coating is applied to the dosage form. In this example, the top of the dosage

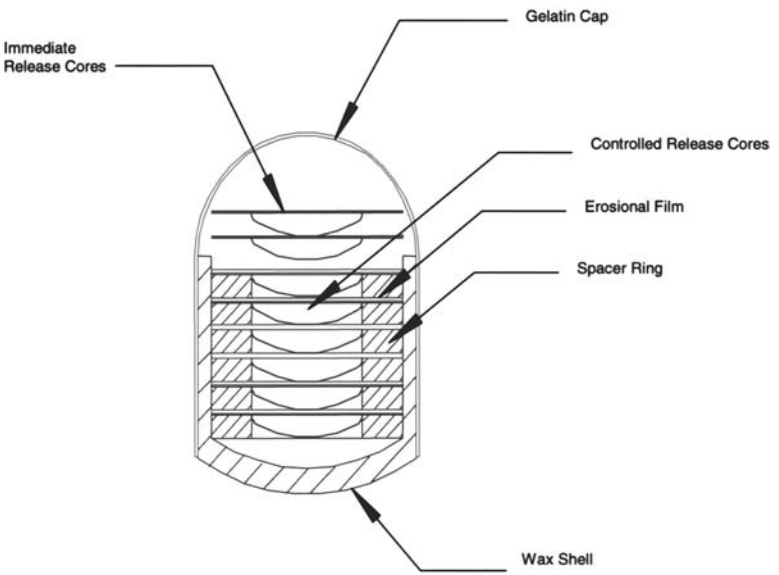


Figure 2 Configuration of an eight-layer dosage form. In this example, the top two layers contain immediate-release cores while the remaining six layers are sandwiched between erosional controlled-release films. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

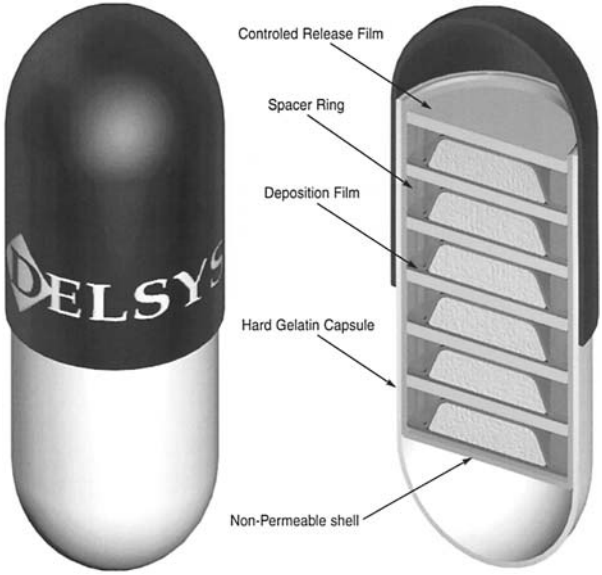


Figure 3 A six-layer dosage form housed in a gelatin capsule. (See color insert.)

form is not coated, and is therefore available for drug release. Pulsatile release is achieved if the layers dissolve sequentially. Figure 3 shows a variation wherein the controlled-release element is enclosed inside a gelatin capsule.

The following variables affect release rate in these systems: (a) rate-controlling film composition, (b) amount of drug per layer, (c) number of layers, (d) inclusion of immediate release elements, and (e) the extent of coverage by an impermeable coating. One benefit of this approach is that the design variables are independent of one another and components can be tested separately, which simplifies formulation. Another benefit is that the rate-controlling elements that dominate the release kinetics are isolated from the drug. This further simplifies formulation, and minimizes exposure of the drug to excipients.

IV. RESEARCH AND DEVELOPMENT

Initial work on the controlled-release dosage forms focused on the identification of polymer films suitable for controlling drug dissolution. Diffusion cells were used to screen polymeric films for potential suitability in the controlled-release dosage form. To identify acceptable polymer films, acetaminophen was used as

Copyright © 2003 Marcel Dekker, Inc.

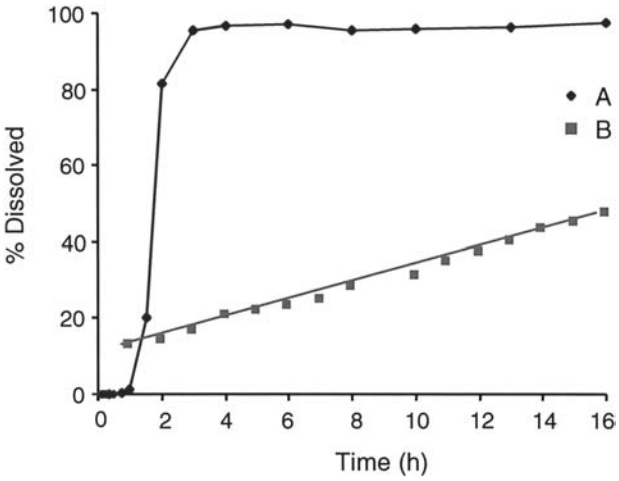


Figure 4 Transport of acetamenophen solution (pH 6.8) across two different films. Film A is a 180-μm-thick cellulose-based film while Film B is composed of polyethylene oxide at the same thickness. (See color insert.)

a marker compound during screening, and the media was pH 6.8 USP buffer solution [2].

Figure 4 shows the screening results for two rate-controlling film candidates. Film A was relatively impermeable for approximately 1 h after exposure to the media, after which time, release was rapid and complete within another 2 h. In contrast, Film B released drug at a relatively constant rate for >16 h. The performance of Film A suggests it might be most suitable for a pulsatile release system when used in series.

Several batches of the controlled-release system were prepared and evaluated by dissolution. Dissolution studies were performed in a USP II apparatus with pH 6.1 or pH 6.8 phosphate buffer at 37.4°C and 50 RPM, using high-performance liquid chromatography analysis. Further development work was performed using Delsys Client Compound Number 30204 (CCN 30204), which is used as an adjunctive for chemotherapy.

A. Demonstration of Pulsatile Release

As stated previously, it is possible to prepare controlled-release dosage forms to provide pulsatile dissolution profiles. This feature is demonstrated in Figure 5, which shows the dissolution data of a three-layer system. It is seen that one-third of the total dose is released at approximately 3-h intervals. The number and

Copyright © 2003 Marcel Dekker, Inc.

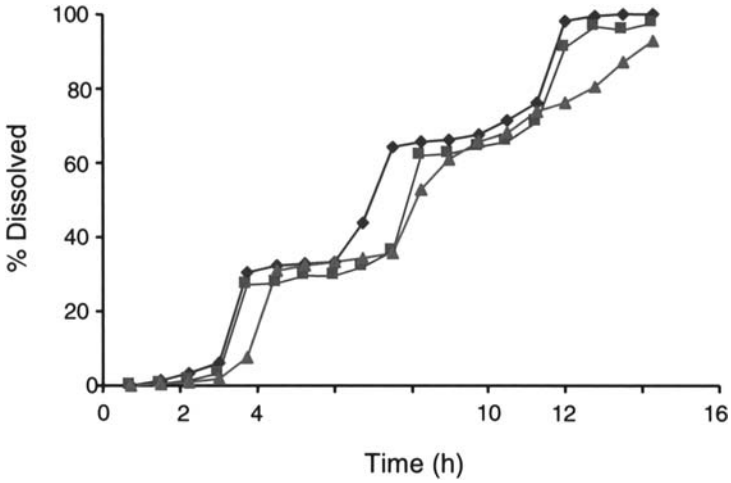


Figure 5 Dissolution of CCN 30204 from a three-layer dosage form at pH 6.1. The dosage form contained 8 mg of active in each layer. Each curve represents a single dosage form. (See color insert.)

duration of each pulse can easily be controlled by the composition of the films and the number of drug-containing layers used.

B. Effect of Rate-Controlling Film Composition

In Figure 6, dissolution was performed on dosage forms prepared with the same rate-controlling films tested in the screening studies (see Fig. 4). Thus in one case, the rate-controlling film was prepared from the cellulosic material while the other formulation was prepared with polyethylene oxide film. The correlation of data indicates that component screening can be used to select films for faster or slower rates of dissolution.

C. Effect of Extent of Coverage by the Impermeable Coating

Using another model drug (theophylline), the effect of varying the surface area of the dosage system available for dissolution has been studied. To compare surface area effects, one device was prepared as described previously wherein release can occur only through one opening in the device. In a second case, the available area for dissolution was doubled by developing a formulation of the same size, but with both the top and bottom surfaces uncoated (and therefore available for dissolution). Figure 7 shows a comparison of the two five-layer

Copyright © 2003 Marcel Dekker, Inc.

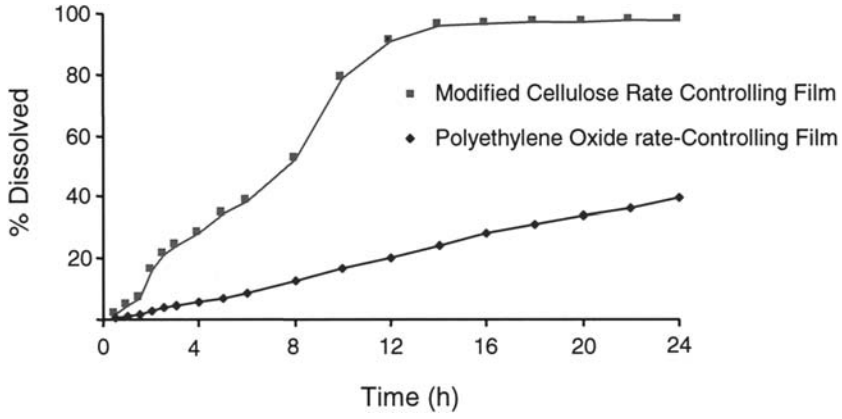


Figure 6 Dissolution of CCN 30204 from a six-layer dosage form at pH 6.8. Both formulations contained 4 mg of active per layer for a total of 24 mg per dosage form. Different rate-controlling film formulations were used (cellulosic or polyethylene oxide). Each curve represents the average of three samples. (See color insert.)

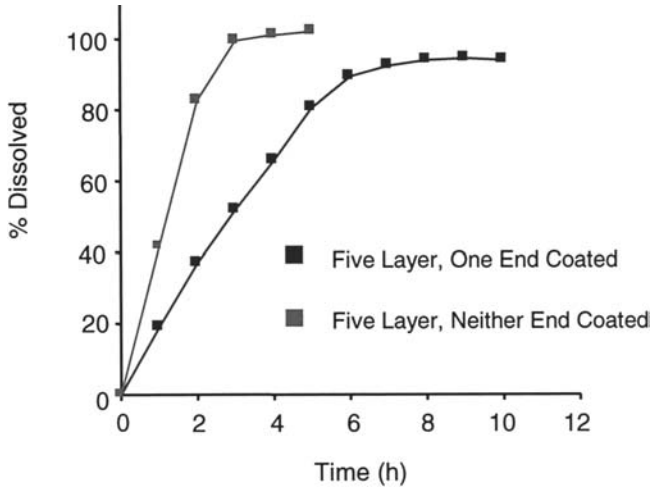


Figure 7 Dissolution of theophylline from a five-layer dosage form. These layers each contained 5 mg of active drug. Each curve represents the average of three separate dosage forms. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

systems wherein increasing the area available for dissolution increases the dissolution rate.

D. Effect of Thickness of Rate-Controlling Film and Number of Layers

It has also been demonstrated (data not shown) that the thickness of the rate-controlling film can be adjusted to alter the release rate of these systems.

V. ANIMAL STUDY

An in vivo study was conducted with CCN 30204 using pigs as an animal model. The objective of this study was to evaluate the absorption profile of CCN30204 from the Tackson CR dosage form (which utilizes the Accudep technology) compared with an immediate-release formulation (solution) of the drug. The controlled-release dosage form was designed to provide an apparent constant absorption of the drug such that the plasma concentration over time would be relatively constant. The solution (24 mg, Q8h $\times 3$) was administered intraduodenally. The controlled-release dosage form (a six-layer formulation containing a total of 24 mg) was also administered intraduodenally. Six pigs were each surgically prepared with two vascular catheters and a duodenal cannula. One catheter was implanted into the right jugular vein, the second into the left internal jugular vein. Both formulations (solution and controlled release) were administered via cannula directly into the duodenum. Pigs were fed ad libitum until being starved overnight (16–20 h) prior to surgery. On the dosing day, the morning feed was withheld from the pigs and they received three-quarters of the total daily ration approximately 4 h after dosing with the controlled-release system or 4 h after the first dose of the solution. Plasma samples were analyzed by LC/MS-MS. The dosage forms were recovered upon elimination from the animal to provide transit time estimates as well as estimates of the extent of drug release. A stability study was conducted with this batch of dosage forms.

The mean plasma levels following intraduodenal administration of the solution and the controlled-release system are shown in Figure 8. While the relative bioavailability of CCN 30204 from the controlled-release dosage form was less than that from the immediate-release solution, these data generally support the fact that drug was released over an extended period of time, and as a result, absorption was prolonged and subsequent blood levels were elevated over a 24-h period. This controlled-release system did not show "dose dumping" but did provide significant release extension. Also, $>90\%$ of the dose was released. No degradation or change in dissolution of the product was observed after 3-months storage at 40°C, 75% RH.

Copyright © 2003 Marcel Dekker, Inc.

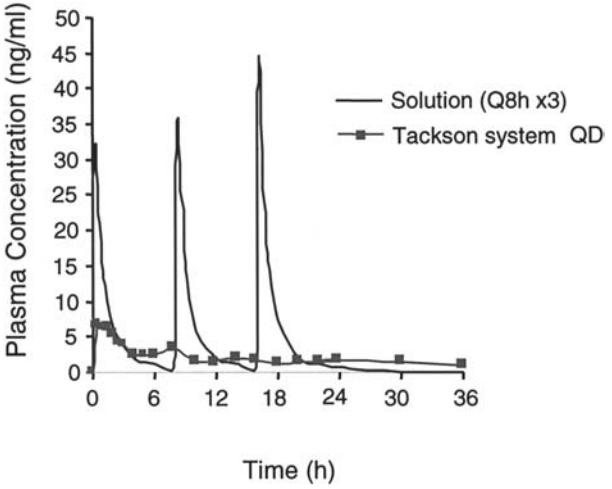


Figure 8 Blood levels of CCN 30204 in pigs. The six-layer dosage form is compared with a three times a day administration of an oral solution. The dosage forms contained 4 mg of CCN 30204 per layer, for a total of 24 mg. (See color insert.)

VI. REGULATORY ISSUES

The controlled-release delivery system under development should not encounter any significant regulatory hurdles. The dosage form is composed entirely of compendial excipients, all of which are approved for oral consumption. The size of the dosage form is within the acceptable range as well.

VII. TECHNOLOGY POSITION/COMPETITIVE ADVANTAGE

The controlled-release system under development by Delsys has a number of advantages over existing technologies. These advantages are inherent in the design features of the dosage form. Some of the principles that can be exploited in the design of dosage forms using the Accudep technology are diffusion barriers, drug binding, slow dissolution, and osmotically modified release. In applying these types of release-modifying mechanisms, attention must be given to some of the features required to modify drug release from a pharamaceutical delivery system, i.e., the multiple-unit principle, complete release after *X* hours, release independent of the hydrodynamics and the environment present in the gastrointestinal tract, reproducibility of manufacture, and release characteristics. The release

Copyright © 2003 Marcel Dekker, Inc.

rate may be constant or may gradually decrease with time. Conversely, release rates can be increased over time to overcome relatively slow absorption from the colon. Using the Accudep technology, selection of the appropriate substrate for the Accudep core or finished product is of paramount importance in developing accurate drug release. For example, retardation of drug release can be affected by utilizing polymer films that have very low permeability coefficients. Therefore, by varying the level of permeability, various rates of drug release can be obtained from a single platform design.

VIII. FUTURE DIRECTIONS

Further studies are underway to determine the range of possibilities of the Delsys controlled-release dosage form. Based on the outcome of these studies, some improvements or modifications will be made in the system. Overall, an effort to reduce the size (in particular the height of the dosage form) is underway. All these improvements are being made consistent with the ability to manufacture these dosage forms at an acceptable cost and speed.

ACKNOWLEDGMENTS

We wish to thank all of the technical team members who participated between Delsys Pharmaceutical and Elan. The in vivo study was conducted by Elan Pharmaceutical Technologies (now Elan Drug Delivery).

REFERENCES

1. SS Chrai, B Singh, M Kopcha, R Murari, S Sun, N Kumar, N Desai, A Levine, H Rivenburg, G Kaganowicz. Electrostatic dry deposition technology. Pharm Tech 4:17–20, 1998.
2. G Kupperblatt, A Katdare, G Slack, J-C Chen, M Karetny, S Chrai. Oral delivery using a novel controlled release technology: system design and materials selection. Proc Int Symp Control Rel Bioact Mater 27:1226–1227, 2000.

Copyright © 2003 Marcel Dekker, Inc.

9
Osmotically Controlled Tablets

Patrick S. L. Wong, Suneel K. Gupta, and Barbara E. Stewart
ALZA Corporation, Mountain View, California, U.S.A.

I. INTRODUCTION

Osmotically controlled tablets use osmosis, the natural movement of water through a membrane, to control drug delivery within the gastrointestinal tract. An implantable osmotic injector capable of delivering fluid at a constant rate for weeks was first proposed in 1955 by Rose and Nelson [1]. ALZA Corporation (Mountain View, CA) pioneered the solid tablet osmotic dosage form (the Oros® system) [2–4] in the 1970s, various configurations of which have been marketed since 1983 generating sales of about $1.5 billion in 1999. Currently, more than 10 products using Oros technology are marketed for the treatment of various conditions (Table 1).

Oros technology can deliver up to 750 mg of certain drugs, including compounds with a wide range of solubilities, at continuously controlled rates for up to 24 h. Compared with other oral controlled-delivery technologies, such as matrix-type and micropellet systems that may be affected by pH, food, and motility in the gastrointestinal environment, since drug in the system core is protected from the gastrointestinal environment and the semipermeable membrane limits the passage of ions, drug release is not affected by motility, pH, or the presence of food. Thus, Oros systems provide a more consistent drug release, particulary in the colon.

II. THEORY OF OPERATION

The basic osmotically controlled tablet is shown in Figure 1. It consists of an osmotic drug-containing core surrounded by a semipermeable membrane with

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Currently Marketed Osmotically Controlled Tablets

Alpress® LP (prazosin), once-daily extended-release tablet sold in France for the treatment of hypertension (Novartis Pharmaceuticals Corporation, East Hanover, NJ)
Cardura XL® (doxazosin mesylate), sold in Germany for the treatment of hypertension (Pfizer Inc, New York)
Concerta™ (methylphenidate HCl), once-daily extended-release tablet for the treatment of attention deficit hyperactivity disorder (ADHD) (ALZA Pharmaceuticals, Mountain View, CA)
Covera-HS® (verapamil), a Controlled Onset Extended Release (COER-24™) system for the management of hypertension and angina (GD Searle & Co, Chicago, IL)
Ditropan XL® (oxybutynin chloride), extended-release tablet for the once-daily treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency (ALZA Pharmaceuticals, Mountain View, CA)
DynaCirc CR® (isradipine), once-daily extended-release tablet for the treatment of hypertension (Novartis Pharmaceuticals Corporation, East Hanover, NJ)
Glucotrol XL® (glipizide), extended-release tablet used as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes (Pfizer Inc, New York)
Procardia XL® (nifedipine), extended-release tablet for the treatment of angina and hypertension (Pfizer Inc, New York)
Sudafed® 24 Hour (pseudoephedrine HCl), for the temporary relief of nasal congestion due to the common cold, hay fever, and other respiratory allergies, and nasal congestion associated with sinusitis (Warner-Lambert Consumer Healthcare, Morris Plains, NJ)
Volmax® (albuterol sulfate), extended-release tablet for relief of bronchospasm in patients with reversible obstructive airway disease (Muro Pharmaceutical, Inc, Tewksbury, MA)
Tegretol® XL (carbamazepine), extended-release tablet for use as an anticonvulsant drug (Novartis Pharmaceuticals Corporation, East Hanover, NJ)

orifices for drug release. In the aqueous environment of the gastrointestinal tract, water is drawn by osmosis across the semipermeable membrane into the system core at a rate controlled by the composition and thickness of the membrane. Drug in solution or suspension is released through the orifices at the same rate that water is imbibed into the system.

The chemical potential of the drug core (μ) can be expressed as follows:

$$\mu = \mu^\circ - v\pi \cong \mu^\circ - RTvC_m \tag{1}$$

where μ° is the chemical potential of water external to the tablet, v is the molar volume of water, π is the osmotic pressure difference between the core and its environment, C_m is the molar concentration of the drug formulation, R is the gas constant, and T is the temperature.

Copyright © 2003 Marcel Dekker, Inc.

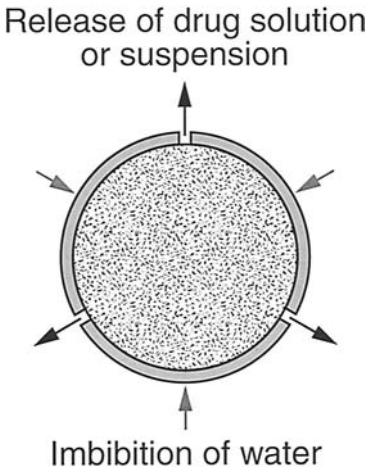


Figure 1 Osmotically controlled tablet.

Equation (1) defines the relationship between the osmotic pressure (π) and the soluble nature of the drug core (C_m).

The release rate ($\dot{M}$) of a single drug core and the volume imbibition rate of water ($\dot{V}$) are calculated as follows:

$$\dot{M} = C\,\dot{V} \tag{2}$$

$$\dot{V} = (A/h)\,k\pi \tag{3}$$

where $\dot{M}$ is the mass release rate, $\dot{V}$ is the volume imbibition rate of water, C is the mass concentration of the drug in solution or suspension, A is the membrane area, h is the membrane thickness, and k is the osmotic membrane permeability.

The mass release rate ($\dot{M}$) is constant, or at steady state, if the core is maintained at saturation (i.e., when C equals the solubility of the saturated drug solution).

An osmotically controlled tablet with a multicompartment core [5] is shown in Figure 2. When the various layers in the core contain different drug concentrations, the mass release rate is calculated as follows:

$$\dot{M} = \left[\left(\frac{A_1}{h} K_{\Pi_1}\right) + \left(\frac{A_2}{h} K_{\Pi_2}\right) + \left(\frac{A_3}{h} K_{\Pi_3}\right) + \ldots \left(\frac{A_n}{h} K_{\Pi_n}\right)\right] \cdot C_n = \dot{V}_{C_n} \tag{4}$$

Copyright © 2003 Marcel Dekker, Inc.

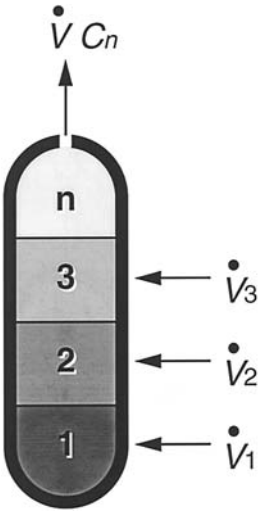


Figure 2 Osmotic drug delivery system with a multicompartment core.

The bottom layer in a multicompartment system contains no drug ($C_1 = 0$) and usually serves as a push engine displacing drug in the core. Subsequent layers may contain different drug concentrations ($C_2 \neq C_3 \neq C_4$). When the drug suspensions or solutions from these layers are pushed out in series, different release profiles can be generated (Fig. 3). These release profiles and the corresponding pattern of drug concentrations in the core layers are described below.

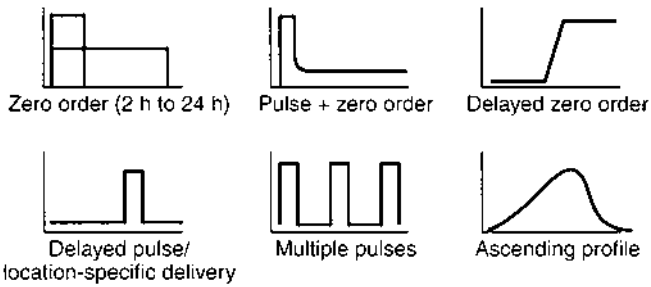


Figure 3 Examples of delivery profiles possible with Oros systems.

Copyright © 2003 Marcel Dekker, Inc.

Zero order	$C_1 = 0$	$C_2 = C_3 = C_n$
Ascending order	$C_1 = 0$	$C_2 > C_3 > C_n$
Descending order	$C_1 = 0$	$C_2 < C_3 < C_n$
Delaying/zero order	$C_1 = 0$	$C_2 = C_3\ C_n = 0$
Two pulse	$C_1 = 0$	$C_3 = 0\ C_n = C_2$

Drug in the layers of a multicompartment system can be insoluble as long as soluble excipients help to form a suspension during operation.

III. TYPES OF OSMOTIC CONTROLLED SYSTEMS

A. Oros Elementary Osmotic Pump

The basic Oros system, the elementary osmotic pump (EOP), was first described by Theeuwes in 1975 [2]. It consists of a drug-containing core, a semipermeable membrane made of water-permeable cellulose polymers, and orifices from drug release. Water is drawn into the system by osmosis, displacing drug in the core, which is then released through the orifices [2,6].

The release profile of an EOP system declines when solid drug in the core is depleted; therefore, a drug with high solubility cannot maintain prolonged zero-order release. A drug with low solubility, however, lacks the ability to generate sufficient osmotic pressure, leaving moderately soluble drugs as the most appropriate for the EOP system.

B. Oros Push-Pull Osmotic System

The Oros Push-Pull™ system uses a multicompartment core to deliver drugs of any solubility [3,6]. The basic Push-Pull system resembles a simple tablet in shape and has two layers. The first layer contains the drug substance, osmotically active hydrophilic polymers, and other excipients. The second layer, or push layer, contains a hydrophilic expansion polymer and other osmotically active agents and tablet excipients (Fig. 4). To assist in the transport of drug, the push layer expands, acting like a piston to gently push the drug suspension or solution out through the orifice.

Adjustments to the composition and thickness of the system's semipermeable membrane are made to achieve a precise delivery rate that is independent of gastrointestinal pH (Fig. 5) and external agitation (Fig. 6).

C. Patterned Drug Delivery

The basic Oros EOP and Push-Pull designs, which allow zero-order delivery of drugs of any solubility, can be modified to provide patterned release (e.g., pulsed, ascending, delayed).

Copyright © 2003 Marcel Dekker, Inc.

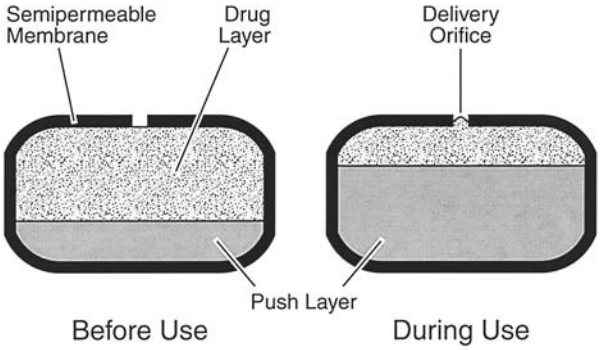


Figure 4 Cross-section of an Oros Push-Pull (bilayer) system before and during use.

One variation on the Push-Pull system is the controlled-onset extended-release (COER) design. The Push-Pull system is modified, so delivery of drug is delayed to provide peak plasma levels at an appropriate time. A slowly hydrating placebo layer is added around the system's core to delay the influx of water into the drug and push layers. When hydration occurs, the placebo delay layer hydrates first and is released ahead of the drug formulation.

Another variation on the Push-Pull system, the capsule-shaped tablet, makes possible patterned delivery of one or more drugs (examples include as-

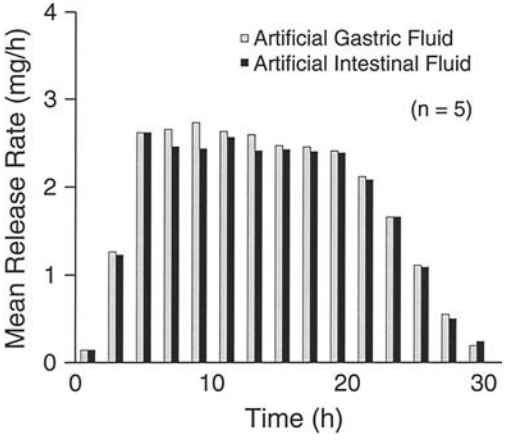


Figure 5 Release rate from Procardia XL 60 mg exposed to artificial gastric and intestinal fluids.

Copyright © 2003 Marcel Dekker, Inc.

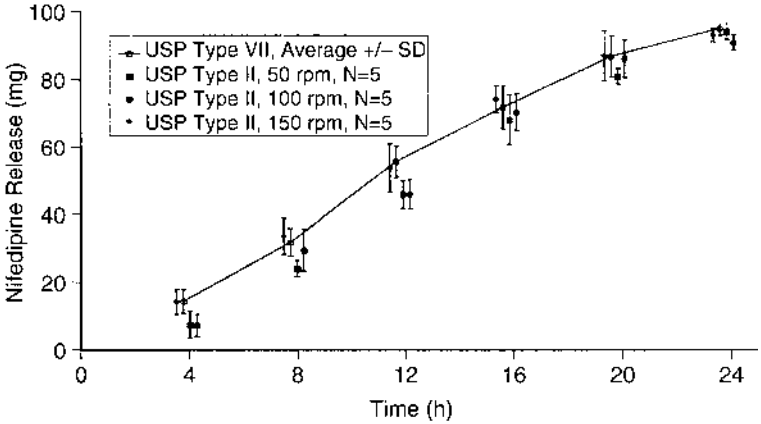


Figure 6 Cumulative amount of drug released from Procardia XL 90 mg as a function of stirring rate.

cending and pulsed delivery). The capsule-shaped tablet consists of the multicompartment core, semipermeable membrane, and delivery orifice of the basic Push-Pull system and uses the same osmotic principles, but the capsule shape allows more versatility in patterned delivery (Fig. 7). In addition, by increasing the surface-area-to-volume ratio of the core, the capsule-shaped tablet can provide an increasing rate of drug delivery over time.

IV. ADVANTAGES OF THE OROS SYSTEMS

Osmotically controlled tablets can provide many benefits, including delivering drug at an optimal rate, at an optimal time, or in a specified pattern. The following examples demonstrate some of the advantages gained by using osmotically controlled tablets to deliver drugs.

A. Nifedipine

When administered from immediate-release liquid capsules, nifedipine, an insoluble calcium channel blocker, is rapidly absorbed, resulting in high initial peak plasma drug concentrations. A single dose of immediate-release nifedipine has been found to increase heart rate by 12–17% and, with longer-term administration, by 6–9% [7]. Infusion studies by Kleinbloesem and colleagues [8] demonstrated that a slow induction of nifedipine not only eliminates postdose tachycar-

Copyright © 2003 Marcel Dekker, Inc.

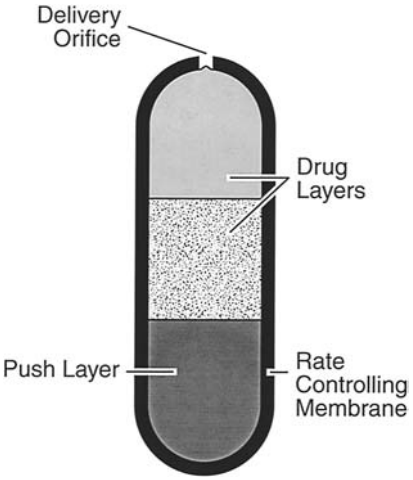


Figure 7 Cross section of an Oros Push-Pull trilayer capsule-shaped tablet with two drug layers.

dia by also significantly reduces systolic and diastolic blood pressure compared with rapid induction of the drug. Figure 8 shows the plasma profile of a once-daily dose of nifedipine delivered by an Oros Push-Pull system (Procardia XL®). As Figure 8 shows, a single 60-mg dose of Procardia XL (administered once a day) provides a steady plasma level throughout the day and eliminates the rapid rise in plasma concentration seen with immediate-release nifedipine (20 mg administered three times a day).

B. Oxybutynin Chloride

Oxybutynin chloride, an antispasmodic, anticholinergic agent, is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. In an open-label, multiple-dose, two-way crossover pharmacokinetic study, a once-daily Oros Push-Pull formulation of oxybutynin chloride (Ditropan XL®), when compared with immediate-release oxybutynin chloride, demonstrated a relative bioavailability of 153% and a higher drug-to-metabolite ratio [9]. The higher bioavailability of the Oros formulation suggests less first-pass metabolism and may be explained by the site of drug release. Oxybutynin is metabolized in the liver and gut wall primarily by the cytochrome P450-mediated oxidation enzyme CYP3A41. Oros oxybutynin chloride may reach the colon 3–5 h after the dose is taken, and oxidation by the P450-mediated enzyme may not be as extensive in the colon as it is in the small intestine [9].

Copyright © 2003 Marcel Dekker, Inc.

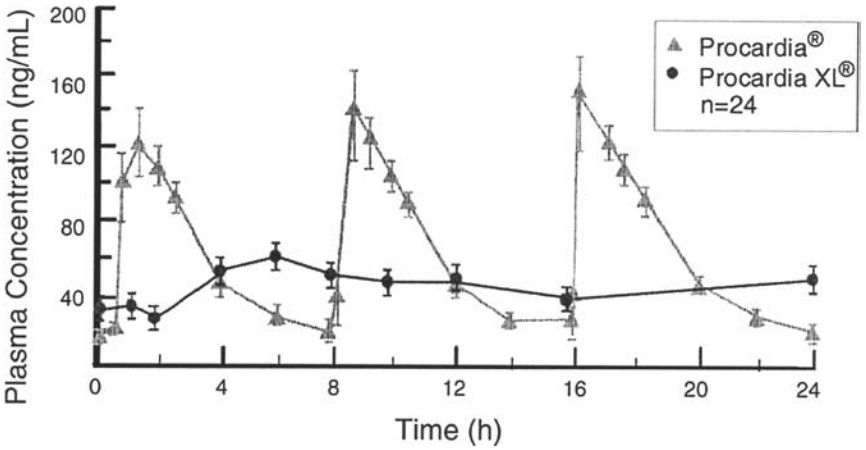


Figure 8 Steady-state plasma profiles of immediate-release nifedipine (three times a day) and Procardia XL on day 5.

In the same study, fewer subjects reported dry mouth, an anticholinergic side effect, with Ditropan XL compared with immediate-release oxybutynin chloride [9]. Possible explanations given by the authors for the lower incidence of dry mouth with the Oros formulation were reduced exposure to the drug's metabolite, *N*-desethyloxybutynin, and the formulation's plasma profile. Like Procardia XL®, Ditropan XL provides a constant plasma level that eliminates the peaks and troughs of immediate-release dosing.

C. Methylphenidate HCl

Conventional treatment for attention deficit hyperactivity disorder (ADHD) consists of immediate-release methylphenidate HCl administered two or three times a day to cover school and afterschool periods. Swanson and colleagues [10] reported that methylphenidate HCl delivered to give a flat plasma profile lost efficacy in the afternoon; however, when methylphenidate HCl was delivered to give an ascending plasma profile, efficacy was maintained throughout the day. The capsule-shaped variation on the Oros Push-Pull system and a multicompartment core were used to provide an ascending plasma profile for Oros methylphenidate HCl (Concerta™). Figure 9 shows the plasma profile of Concerta administered once a day compared with the plasma profile of immediate-release methylphenidate administered three times a day in adults.

Osmotically controlled tablets may also provide the convenience of fewer doses, making compliance with dosing regimens easier. For methylphenidate

Copyright © 2003 Marcel Dekker, Inc.

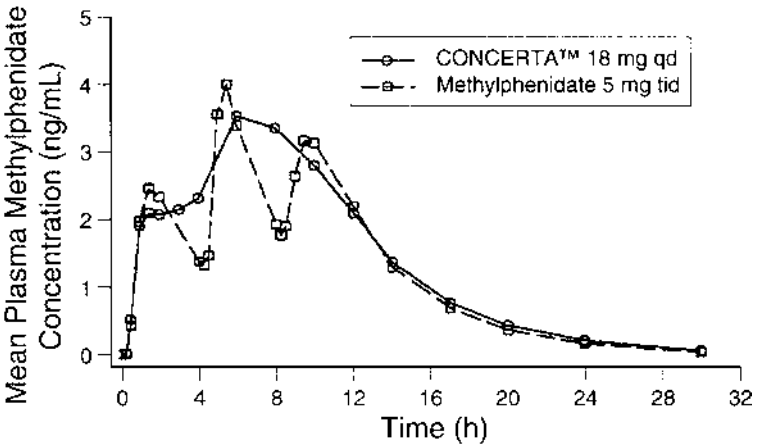


Figure 9 Mean methylphenidate plasma concentrations in 36 adults following Concerta 18 mg (once a day) and immediate-release methylphenidate 5 mg (three times a day) administered every 4 h.

HCl, a Schedule II drug, once-a-day dosing at home may decrease the potential for drug diversion at school.

V. NONCLINICAL SAFETY PROGRAM

During development, the toxicology program for a new Oros system evaluates the safety of the drug substance, the safety of the excipients used in the Oros drug formulation, and the systemic and local (gastrointestinal) tolerability of the drug-containing Oros system. The existing scientific literature on the drug substance and excipients, including the pharmacology, toxicology, and pharmacokinetics of the drug, is reviewed. The anticipated clinical use and proposed development program are considered, along with the applicable International Conference on Harmonisation (ICH) guidelines.

Studies in a typical toxicology program for an Oros product using a drug substance previously approved by the FDA may include:

Oral dosing study of 30–90 days in dogs to evaluate gastrointestinal tolerability and systemic toxicity

In vitro/in vivo drug release rate study to compare the in vivo release profile in the dog with the in vitro release profile

Copyright © 2003 Marcel Dekker, Inc.

Studies determined for the individual drug product, including studies to supplement the database on the drug substance as needed, and 6- or 12-month oral toxicity studies as needed to evaluate the drug's long-term systemic effects

The toxicology programs of three recently developed Oros dosage systems (oxybutynin chloride, methylphenidate HCl, and hydromorphone HCl) included 30-day oral dosing studies in dogs. No gastrointestinal irritation or adverse gastrointestinal events were seen, and systemic toxicity was limited to effects consistent with the pharmacology for high-dose levels of the drugs tested.

VI. SAFETY OF THE DOSAGE FORM

Dose dumping (early release of most of the drug dose) is not an issue with Oros systems because the drug core is enclosed within a semipermeable membrane. Defects such as cracks in the membrane would produce only a slight increase in the release rate. The absence of a membrane coating, depending on the drug formulation (i.e., if the drug is soluble), could result in a release rate much higher than the designed rate, but still slower than that of an immediate-release dose.

More than 10 products using Oros technology have been marketed since the first product was introduced in 1983. Numerous clinical trials reported in the literature have demonstrated that Oros products are effective and well tolerated [11–18]. Adverse events associated with Oros products tend to be related to the drug substance [19] rather than to the delivery technology.

VII. IN VIVO/IN VITRO CORRELATION

In vivo/in vitro correlations in dogs and humans have shown that the gastrointestinal environment does not affect the predicted release profile of the Oros system [6].

VIII. MANUFACTURING

Oros is a well-established technology as demonstrated by the number of approved and marketed products. Manufacturing uses mostly standard unit operations, which consist of granulation, tableting, coating, and drilling. Specialized equipment for Oros systems includes a multilayer tablet machine and customized laser drilling facilities.

Copyright © 2003 Marcel Dekker, Inc.

IX. OUTLOOK

Oros configurations in development include the following.

A. Oros Push-Stick Technology

The Oros Push-Stick™ technology is designed for high drug loading (up to 600 mg) of insoluble compounds. The Oros Push-Stick technology provides the greatest benefit for compounds with low water solubility and dosage greater than 150 mg.

The technology in its basic configuration consists of a bilayer capsule-shaped tablet. The Oros Push-Stick system has a much larger orifice than the EOP and Push-Pull systems and, for some drugs, uses a hydrophilic polymer subcoat between the tablet and the semipermeable membrane to facilitate the optimum delivery of the drug. In its basic configuration, the system can deliver drug in a zero-order pattern over an extended period of time. With a multicompartment core, the Push-Stick system can provide patterned drug delivery. For example, two drug compartments separated by a waxy placebo layer, when pushed out in series, provide two-pulse drug delivery.

B. Liquid Osmotic System (L-Oros)

Another variation on the basic Oros technology allows the delivery of liquid drug formulations. A liquid formulation is particularly well suited for delivering insoluble drugs and macromolecules such as polysaccharides and polypeptides. Such molecules require external liquid components to assist in solubilization, dispersion, protection from enzymatic degradation, and promotion of gastrointes-

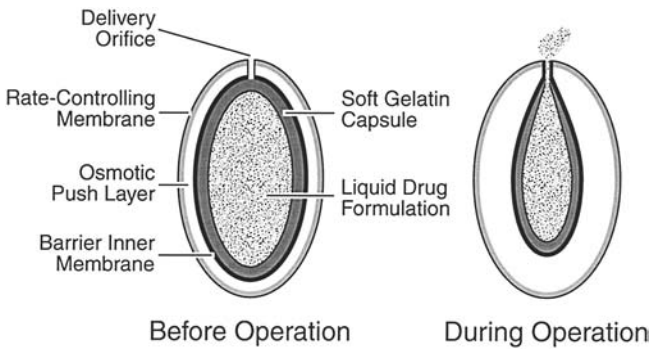


Figure 10 Configuration of L-Oros Softcap System.

Copyright © 2003 Marcel Dekker, Inc.

tinal absorption. The L-Oros® system was designed to provide continuous delivery of liquid drug formulations and improve bioavailability of the drugs.

One type of L-Oros system consists of a soft gelatin capsule (Softcap™) surrounded by a barrier layer, an osmotic push layer, and a semipermeable membrane (Fig. 10). As with other Oros systems, drug is released through a delivery orifice in the semipermeable membrane. Another type of L-Oros system consists of a hard gelatin capsule (Hardcap™) containing a liquid drug layer, a barrier layer, and a push layer surrounded by a semipermeable membrane. The L-Oros Hardcap system was designed to accommodate more viscous suspensions with higher drug loading than would be possible using the Softcap design.

X. FUTURE IMPROVEMENTS

Future improvements to osmotically controlled tablets will focus on patterned and site-specific drug delivery, increased drug loading, improved drug absorption, and delivery of macromolecules.

ACKNOWLEDGMENT

The authors acknowledge Kathleen Ryan for her invaluable editorial contribution.

REFERENCES

1. S Rose, JF Nelson. A continuous long-term injector. Aust J Exp Biol 33:415–420, 1955.
2. F Theeuwes. Elementary osmotic pump. J Pharm Sci 64:1987–1991, 1975.
3. P Wong, B Barclay, JC Deter, F Theeuwes. Osmotic device with dual thermodynamic activity. US patent 4,612,008, 1986.
4. G Santus, RW Baker. Osmotic drug delivery: a review of the patent literature. J Control Rel 35:1–21, 1995.
5. P Wong, F Theeuwes, J Eckenhoff, S Larson, H Huynh. Multi-unit delivery system. US patent 5,023,088, 1991.
6. F Theeuwes, P Wong, S Yum. Drug delivery and therapeutic systems. In: J Swarbrick, J Boylan, eds. Encyclopedia of Pharmaceutical Technology. Vol. 4. New York: Marcel Dekker, 1991, pp. 303–348.
7. D Murdoch, RN Brogden. Sustained release nifedipine formulations: an appraisal of their current uses and prospective roles in the treatment of hypertension, ischaemic heart disease and peripheral vascular disorders. Drugs 41:737–779, 1991.
8. CH Kleinbloesem, P Van Brummelen, M Danhof, H Faber, J Urquhart, DD Breimer.

Copyright © 2003 Marcel Dekker, Inc.

Rate of increase in the plasma concentration of nifedipine as a major determinant of its hemodynamic effects in humans. Clin Pharmacol Ther 41:26–30, 1987.
9. SK Gupta, G Sathyan. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. J Clin Pharm 39:289–296, 1999.
10. J Swanson, S Gupta, D Gunita, D Flynn, D Agler, M Lenner, L William, I Shoulson, S Wigal. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. Clin Pharmacol Ther 66:295–305, 1999.
11. WB White, MF Johnson, HR Black, TD Fakouhi. Effects of the chronotherapeutic delivery of verapamil on circadian blood pressure in African-American patients with hypertension. Ethn Dis 9:341–349, 1999.
12. WH Frishman, S Glasser, P Stone, PC Deedwania, M Johnson, TD Fakouhi. Comparison of controlled-onset, extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. Am J Cardiol 83:507–514, 1999.
13. SD Ross, B Kupelnick, M Kumashiro, FM Arellano, N Mohanty, IE Allen. Risk of serious adverse events in hypertensive patients receiving isradipine: a meta-analysis. J Hum Hypertens 11:743–751, 1997.
14. MA Testa, DC Simonson. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. JAMA 280:1490–1496, 1998.
15. DC Simonson, IA Kourides, M Feinglos, H Shamoon, CT Fischette. Efficacy, safety, and dose-repsonse characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM: results of two multicenter, randomized, placebo-controlled clinical trials. The Glipizide Gastrointestinal Therapeutic System Study Group. Diabetes Care 20:597–606, 1997.
16. RJ Martin, M Kraft, WN Beaucher, F Kiechel, JL Sublett, N LaVallee, J Shilstone. Comparative study of extended release albuterol sulfate and long-acting inhaled salmeterol xinafoate in the treatment of nocturnal asthma. Ann Allergy Asthma Immunol 83:121–126, 1999.
17. TE Wilens. Long-term safety and effectiveness of Concerta (methylphenidate HCl) in children with ADHD. Neurology 54:A420, 2000 (abstract).
18. LL Greenhill. Evaluation of the efficacy and safety of Concerta (methylphenidate HCl) extended-released tablets, Ritalin, and placebo in children with ADHD. Neurology 54:A420, 2000 (abstract).
19. CB Toal, M Motro, MC Baird, P Klinke, S Sclarowski, A Zilberman, A Marmor, WJ Kostuk, C Lotan, A Weiss, P Erne, A Palant, D Stolero, L Belanger, A Turpie. Effectiveness of nifedipine GITS in combination with atenolol in chronic stable angina. Can J Cardiol 15:1103–1109, 1999.

Copyright © 2003 Marcel Dekker, Inc.

10

Three-Phase Pharmaceutical Form—Threeform—with Controlled Release of Amorphous Active Ingredient for Once-Daily Administration

Janez Kerč
Lek Pharmaceutical and Chemical Company, Ljubljana, Slovenia

I. INTRODUCTION

The novel three-phase pharmaceutical form—Threeform—oral delivery system has been formulated to provide controlled release of amorphous active ingredients for once-daily administration. It has been primarily used to formulate a nifedipine once-daily formulation. However, the new technology can be adopted for various active ingredients that demand a controlled-release profile over an extended period of time. US patent No. 6,042,847 for the technology and formulation was granted on March 28, 2000 [1].

II. HISTORICAL DEVELOPMENT

The advantages of controlled-release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of an active ingredient over an extended period of time. This increases patient compliance by reducing the number of administrations to achieve the same clinical results as multiple administrations of an immediate-release formulation of the same drug. These advantages may be attained by a wide variety of methods such as oral

Copyright © 2003 Marcel Dekker, Inc.

controlled-release formulations, transdermal formulations, and inhalation formulations. However, oral controlled-release formulations are probably the most effective and convenient administration route for a wide range of active drug substances.

A disadvantage of the currently available oral extended-release dosage forms is that the active ingredient is usually incorporated in its crystalline form, which can lead to the possibility that the crystalline active can occur in several polymorphic modifications. Since the release rate of the active ingredient depends on polymorphic modifications, the crystal size, and thus the specific surface area of the active ingredient, its dissolution rate is not constant and may change depending on the predominating shapes and size distribution of the crystals.

III. DESCRIPTION OF THE TECHNOLOGY

In Threeform oral delivery systems the active ingredient is transformed to an amorphous form that is stabilized by a mixture of polymers comprising polyvinylpyrrolidone and cellulose ethers of various viscosities. The release of the amorphous active ingredient from the three-phase pharmaceutical dosage form is controlled by diffusion through a gel layer and erosion of the matrix. This is determined by the mixture of water-soluble polymer (polyvinylpyrrolidone), a surfactant, cellulose ethers of various viscosities, and a mixture of mono-, di-, and triglycerides. In addition, the release is influenced by a film coating consisting of an ester of hydroxypropylmethylcellulose with phthalic anhydride or of a copolymerizate based on methacrylic acid and ethyl acrylate.

The amorphous active ingredient is stabilized with polymers. It is dispersed in a mixture of polymers at the molecular level and therefore always possesses the same particle size, the same specific surface area, and, consequently, a constant release rate, which is dependent only on formulation ingredients that are tailored to control the release rate of the amorphous active drug.

A schematic presentation of Threeform oral delivery system is given in Figure 1. The first phase of the three-phase pharmaceutical form comprises an amorphous active ingredient (0), a surfactant (1), the water-soluble polymer polyvinylpyrrolidone (2), and a cellulose ether (3). The second phase of the three-phase pharmaceutical form comprises a cellulose ether (4) and, optionally, a mixture of mono-, di-, and triglycerides (5) and other ingredients common to solid dosage forms. The third phase comprises a double film coating. The first film coating consists of an ester of hydroxypropylmethylcellulose with phthalic anhydride or a copolymerizate based on methacrylic acid and ethyl acrylate. The second film coating is a color coating to protect the core from light and consists of

Copyright © 2003 Marcel Dekker, Inc.

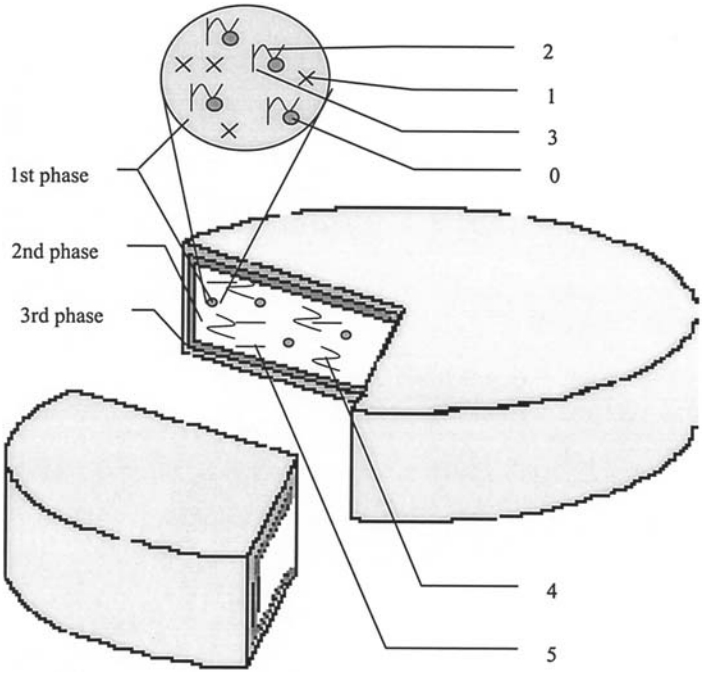


Figure 1 Schematic presentation of Threeform (see text for description of numbers).

cellulose ethers as film formers and other additives such as plasticizers, pigments, lakes, talc, and so forth.

IV. RESEARCH AND DEVELOPMENT

The Threeform oral delivery system is especially suitable for active ingredients that exist in the amorphous form, or in one or more polymorphic forms that exhibit poor solubility in crystal form (depending on its polymorphic form, particle size, and specific surface area). The active ingredient is converted into its amorphous form during the manufacturing process of the three-phase pharmaceutical form. The amorphous form of the active ingredient is confirmed by means of an X-ray diffraction method (Fig. 2).

Nifedipine, a vasodilatory drug from the group of dihydropyridine calcium antagonists, was used as a model drug for incorporating into the Threeform oral

Copyright © 2003 Marcel Dekker, Inc.

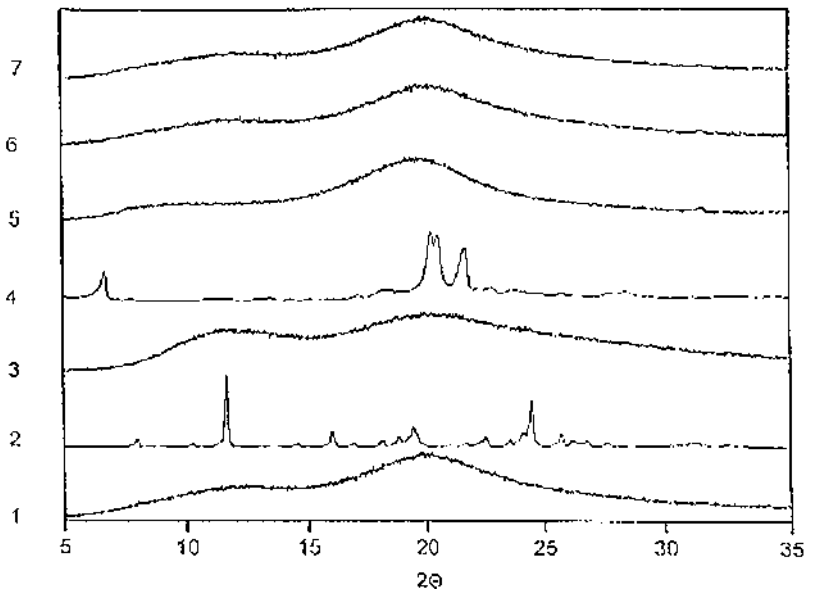


Figure 2 X-ray diffraction patterns: (1) granulation representing the first phase of three-phase pharmaceutical form, (2) nifedipine, (3) polyvinylpyrrolidone, (4) sodium laurylsulfate, (5) hydroxypropylmethylcellulose, (6) and (7) sieved granulation.

delivery system. Nifedipine has at least three polymorphic forms [2] whose solubilities are dependent on their particle size and specific surface area.

A. Manufacturing Process

The Threeform manufacturing process is shown in Figure 3. In the first step of the preparation of the Threeform oral delivery system, an active ingredient, a surfactant, and the water-soluble polymer polyvinylpyrrolidone are dissolved in an organic solvent.

This is then sprayed onto cellulose ether in the fluid bed granulator. As mentioned earlier, the active ingredient can be used in any of its amorphous or polymorphous forms. It is at this stage in the process that coprecipitation occurs and the active drug is converted into an amorphous form that is stabilized by the water-soluble polymer polyvinylpyrrolidone and a cellulose ether.

The second step is conducted in such a manner that the granulate obtained in the first step is homogeneously mixed with a cellulose ether and other adjuvants generally used in the preparation of solid pharmaceutical forms and the components are compressed into tablets.

Copyright © 2003 Marcel Dekker, Inc.

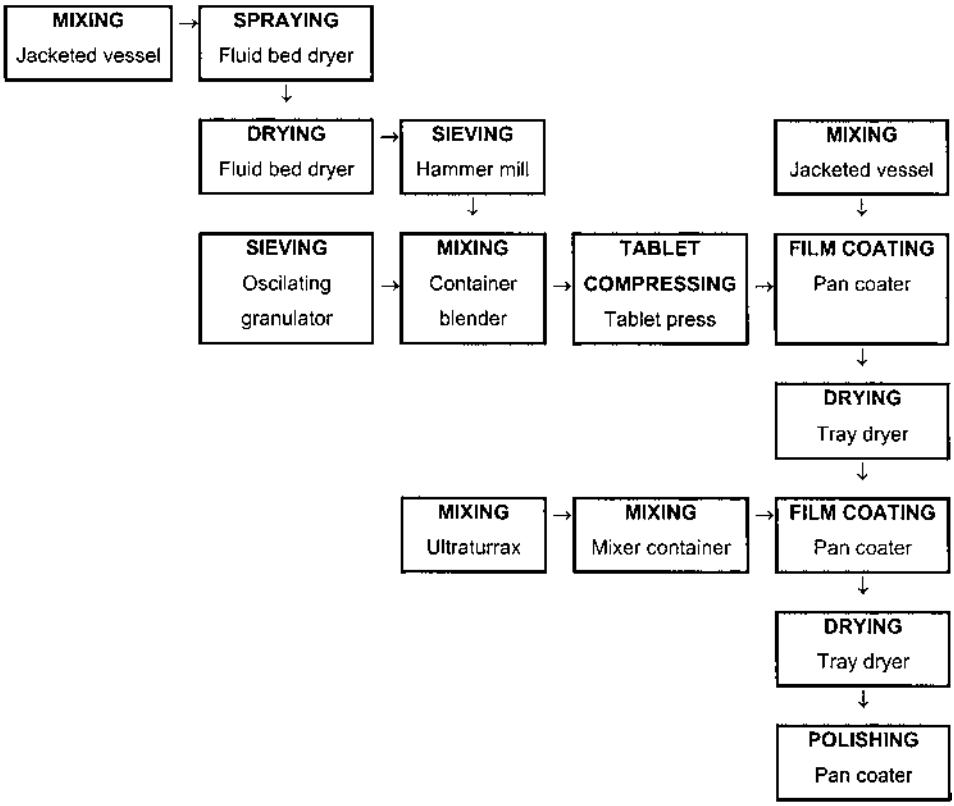


Figure 3 Formulation scheme for Threeform.

In the third step the film coating is prepared by dissolving the polymers in a single organic solvent, in mixtures of organic solvents, or in mixtures thereof with water. Plasticizers such as polyethylene glycols of various molecular weights, triacetine, triethyl citrate, dibutyl sebacate, and so forth are then added to the polymer solution. The coating is then sprayed onto the cores in a coating pan. Finally, the color coating is sprayed onto the delivery system to protect it from the effects of light.

B. In Vitro Studies

Dissolution studies (USP Paddle method, wire helix Vankel) were conducted in 0.1 *N* HCl with 1.0% sodium lauryl sulfate, 1000 mL (0–2 h) and/or in phosphate

Copyright © 2003 Marcel Dekker, Inc.

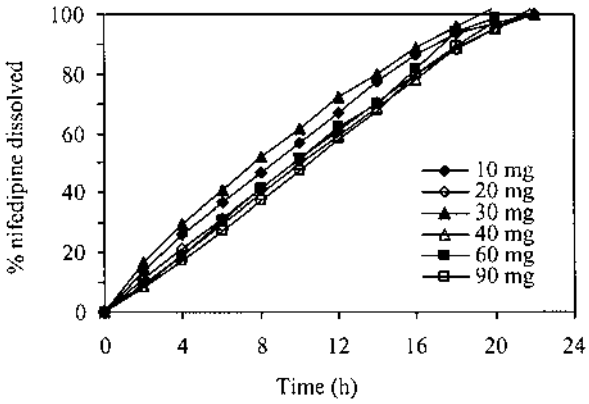


Figure 4 Nifedipine dissolution profile from tablet cores representing the first and the second phase of Threeform containing different amounts of nifedipine.

buffer pH 6.8 with 1% sodium lauryl sulfate, 1000 mL (2–24 h); rotation speed: 75 rpm; assay method: UV 340 nm. With nifedipine as an active ingredient, Threeform oral delivery system prepared according to the method described above yielded constant and controlled in vitro release (Fig. 4). The nifedipine dissolution profile was almost independent of the amount of nifedipine incorporated in the matrix tablet (Fig. 4) [3,4].

Viscosity and substitution type of HPMC had a significant effect on the nifedipine dissolution profile (Fig. 5). Using HPMC with viscosity of 4000 cP, fillers such as Ludipress or Ca_2HPO_4 can cause faster dissolution after 12 h of dissolution owing to faster disintegration of the HPMC matrix (Fig. 5: 2/C, 2/D) [3]. A larger amount of HPMC was necessary to form a strong hydrogel that eroded slowly and provided a constant release over 24-h dissolution assay (Fig. 6) [3].

C. In Vivo Studies

In vivo fasted, nonfasted, and steady-state studies were performed in 30–40 (60- and 90-mg dose) and 12 (30-mg dose) male volunteers. Blood samples were withdrawn at different intervals up to 60 h after administration of a Threeform nifedipine oral delivery system. Plasma samples were assayed using a gas chromatographic method with an electron capture detector.

After a single administration of the Threeform nifedipine oral delivery system, plasma concentrations were observed to be fairly constant over a 24-h period in fasted patients (Fig. 7) and exhibited no peak levels (which are typically ob-

Copyright © 2003 Marcel Dekker, Inc.

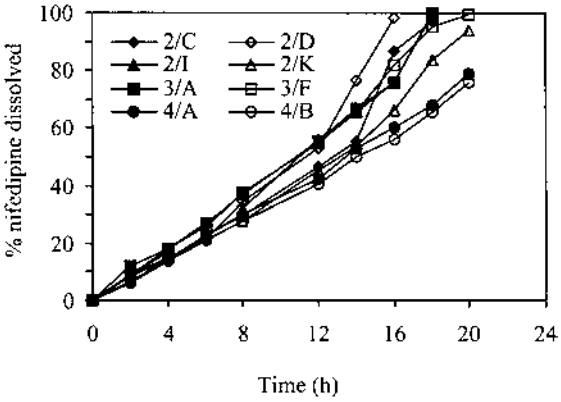


Figure 5 Nifedipine dissolution profile from tablet cores containing 60 mg of nifedipine:

2/C—20% HPMC E4M, 8% Ludipress;
2/D—20% HPMC E4M, 8% $CaHPO_4$;
2/I—20% HPMC K4M, 8% Ludipress;
2/K—24% HPMC E4M, 8% Ludipress;
3/A—24% HPMC K4M, 8% Ludipress;
3/F—20% HPMC K15M, 8% Ludipress;
4/A—17% HPMC K100M, 8% Ludipress;
4/B—17% HPMC K100M, 8% Emcompress.

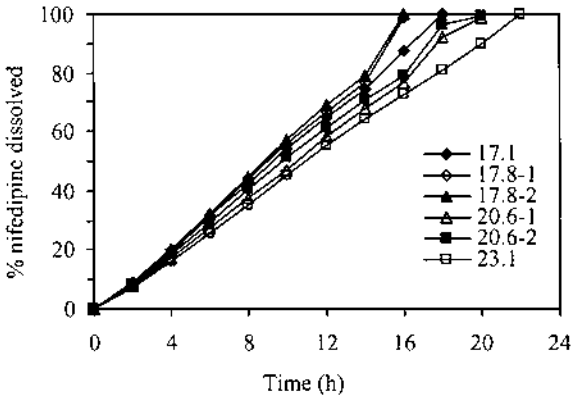


Figure 6 Nifedipine dissolution profile from tablet cores containing 60 mg of nifedipine and various amounts (%) of HPMC K100M (tablet hardness: 1. 7–10 kP, 2. 11–13 kP).

Copyright © 2003 Marcel Dekker, Inc.

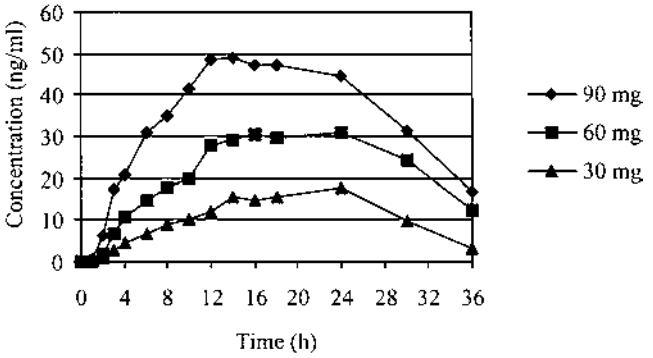


Figure 7 Mean plasma concentrations for nifedipine 30 mg, 60 mg, and 90 mg Threeform—fasted study.

served when an immediate-release nifedipine dosage form is administered). Since nifedipine is used in chronic therapy of arterial hypertension, it is essential that therapeutic concentrations are achieved during steady-state administration. This was achieved as shown in Figure 8 [5].

V. CONCLUSION

The ability to deliver a difficult drug like nifedipine, with such a unique profile, demonstrates the capability of the Threeform oral delivery system. Furthermore,

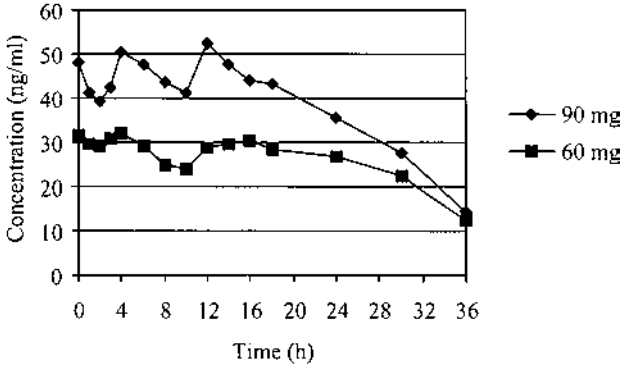


Figure 8 Mean plasma concentrations for nifedipine 60 mg and 90 mg Threeform—steady-state study.

Copyright © 2003 Marcel Dekker, Inc.

the Threeform oral delivery system can be applied to many other active drug substances that exist in amorphous or different polymorphic forms, and especially to those intended for chronic therapy. It can be of special importance for patients with chronic diseases because the Threeform oral delivery system is administered only once daily providing therapeutic concentrations of active ingredient over 24 h, therefore promoting improved patient compliance.

REFERENCES

1. J Kerč, LB Rebič, B Kofler. Three-phase pharmaceutical form with constant and controlled release of amorphous active ingredient for single daily application. US patent 6,042,847, 2000.
2. T Eckert, J Müller. Über polymorphe modifikationen des nifedipine aus unterkühlten schmelzen. Arch Pharm (Weinheim) 310:116–118, 1977.
3. J Kerč, M Mohar, B Kofler. Three-phase pharmaceutical form (Threeform) for nifedipine zero order release. Proc Int Symp Control Rel Bioact Mater 25:912–913, 1998.
4. J Kerč, B Rebič, B Kofler, M Mohar, J Urbančič. Preparation and evaluation of three-phase pharmaceutical form (Threeform) for nifedipine once daily application. Farm Vestn 50:273–274, 1999.
5. J Kerč, J Urbančič. Three-phase pharmaceutical form (Threeform) for nifedipine once daily administration: in vivo studies. Proc Int Symp Control Rel Bioact Mater 26: 879–880, 1999.

Copyright © 2003 Marcel Dekker, Inc.

11

Two Concepts, One Technology: Controlled-Release and Solid Dispersions with Meltrex

Jörg Breitenbach and Jon Lewis
Abbott GmbH & Co. KG, Soliqs drug delivery business, Ludwigshafen, Germany

I. INTRODUCTION

The improvement of the solubility, dissolution rate, and absorption properties of drugs remains a challenging aspect in the development of pharmaceutical products. Therefore, the pharmaceutical interest in new technologies is twofold: to adapt release profiles and to exploit the potential to improve delivery of the drug. Drugs with poor solubility revealed remarkably higher bioavailability when formulated as solid dispersions [1]. The prerequisites of designing proprietary drug delivery systems are to increase the active agent's bioavailability, reduce side effects, overcome solubility barriers throughout the body, and control the duration of the drug's action in the body.

Meltrex™ technology has proved to be an ingeniously simple way of combining both the chance to achieve amorphous embedding of a given drug and at the same time to adjust the release profile from extended release up to zero-order kinetics. The effect of the molecular weight of the matrix polymers on the dissolution profile has been described with special respect to solid dispersions [2,3]. The mechanism of dissolution of molten matrices strongly depends on the choice and combination of polymeric excipients. Another factor predetermining the release rate is the status of the drug, which can be present either as crystalline or amorphous particles, or actually dissolved in the polymeric matrix. In the latter case the active drug is an intrinsic part of the matrix thus influencing its wettabil-

Copyright © 2003 Marcel Dekker, Inc.

ity and release characteristics. The release characteristics may range from predominantly diffusion-controlled to erosion determined.

II. HISTORICAL DEVELOPMENT

Whereas extrusion of wet masses is a standard technology in the field of pharmaceutical production [4], melt extrusion so far has been mainly used in polymer engineering. Melt extrusion for the manufacture of pellets [5,6] and other pioneering work [7] had revealed limitations of melt extrusion and the controlled release of polymer-embedded drugs. Today, Meltrex has made significant progress in developing from a process to a drug delivery technology. The intriguing combination of solid dispersions and controlled release [8] can be of advantage when it comes to decreased absorption because poor solubility of the active limits the availability of the drug in the lower gastrointestinal tract. Moreover, the solid dispersion concept can also offer benefits due to reduced gastric irritation [9]. Additional processing advantages include circumventing the problem of polymorphic forms with different solubility, avoidance of dust, and possible reduction of tablet size.

Solid dispersion systems for drugs have been discussed extensively with particular respect to their methods of preparation, the need to optimize the drug/carrier ratios, and the need to maximize dissolution and absorption rates. Among the suitable polymeric excipients, polyvinylpyrrolidone [10] or its copolymers [11], poly(ethylene-covinylacetate) [12], poly(ethylene-oxide), cellulose-ethers [13], acrylate [14], and other matrices have been applied. There are overlapping areas of excipient combinations when it comes to controlled release. The basic prerequisite for their use in Meltrex is the thermoplasticity of the polymers. The thermoplasticity may be influenced by plasticizers, often a property of the active ingredient itself.

III. DESCRIPTION OF MELTREX TECHNOLOGY

Recently we introduced the Meltrex system to prepare solid dispersion and controlled-release therapeutic systems. The breakthrough was achieved by the availability of a great variety of therapeutic systems using a comparatively simple integrated technological system composed of a broad selection of pharmaceutically approved excipients [15]. The essential advantages of Meltrex are its solvent-free formation process and the dust-free processing environment [16]. Since with solvent processes there are various problems relating to their use (environmental pollution, explosion proofing, and residual organic solvent), measures to counteract these problems are desirable. The same holds for contamination with

Copyright © 2003 Marcel Dekker, Inc.

dust. In addition, Meltrex offers the chance to convert drugs to the amorphous state and is capable of handling actives of different particle sizes as well as amorphous solids or other polymorphic forms. Therefore, Meltrex represents a process that is specifically tailored to deal with these questions.

Figure 1 is a schematic diagram of the extruder typically used in the Meltrex process. The extruder—typically with a conrotating twin-screw configuration—is one core element in the technological system. This equipment consists of a hopper, barrels, screws, kneaders, dies, and kneading device. Feed screws and a kneading paddle are incorporated into the two screws and the screws rotate equiaxially, while the screws accurately engage within the barrels. In addition, the screw elements (the screws and barrels) are of a structure whereby the type and arrangement can be changed, according to the requirements, e.g., viscosity of the plastified mass or sensitivity of the active. Its operation is flexible, easily controlled, and can be well documented.

The temperatures of all the barrels are independent and can be accurately controlled from low temperature (30°C) to high temperature (250°C). During passage through the extruder the mass is heated and the polymer matrix thereby plastified to incorporate the drug material. If solid dispersions are prepared using the Meltrex process, no organic solvents are applied. The drug dissolves in the polymeric matrix, which may therefore be regarded as a highly viscous solvent.

The second core element of the integrated technological system is the device to shape, on line, the molten strand leaving the extruder. Basically, there are two different ways of doing this: (a) calendering, in which the molten strand

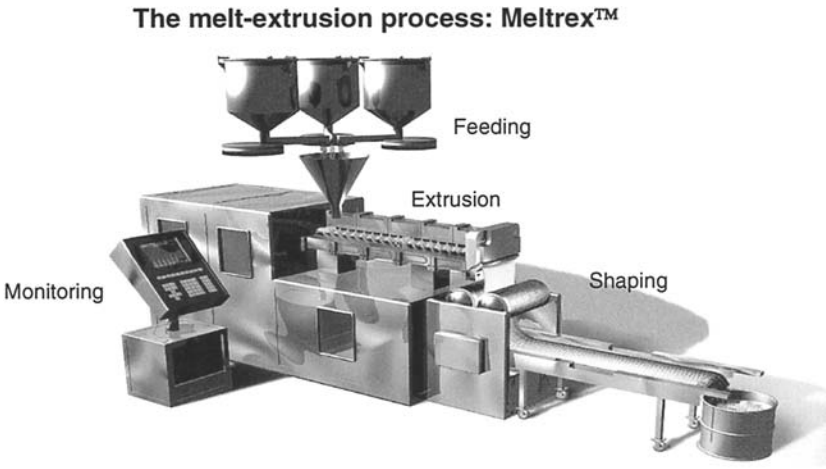


Figure 1 Schematic presentation of the Meltrex process. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

is forced between two calender rollers, thus producing films or sheets that may already contain single tablet cores, and (b) pellet-forming, which may, for example, be a rotating knife cutting spaghetti-like extruded strands.

Overall, the residence time in the extruder is rather short (approximately 2 min) as the process conveys the extruded mass continuously throughout the extrusion channel, thus avoiding heat stress on the active and the respective excipients in the formulation. In addition, oxygen and moisture may be excluded completely—an advantage for drugs sensitive to oxidation and hydrolysis.

IV. RESEARCH AND DEVELOPMENT

A. Controlled Release with Meltrex Technology

Drug material is released in the gastrointestinal tract with contributions from different mechanisms of the Meltrex matrix. Slow erosion as well as erosion after transient swelling at the surface and formation of gel layers can be observed. Generally, different polymer combinations allow different types of retardation, thus giving the process significant degrees of freedom.

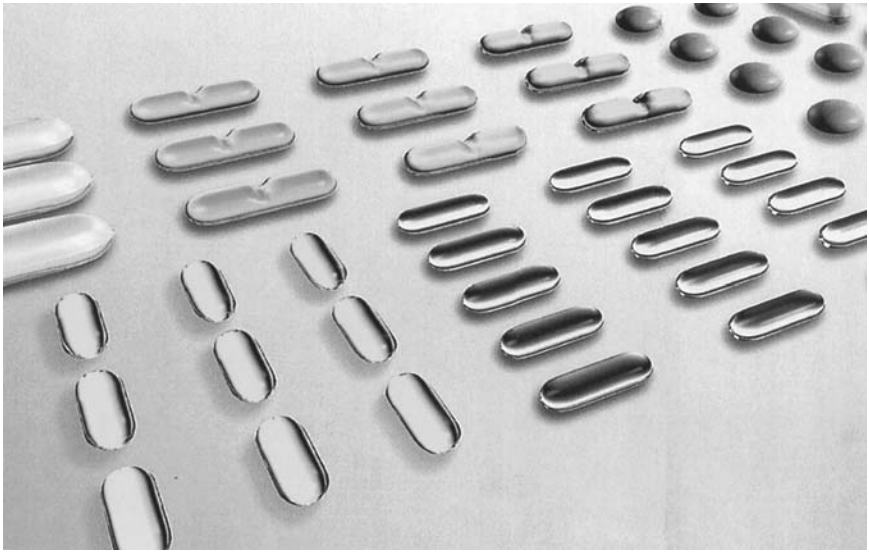


Figure 2 Tablets manufactured by the Meltrex process applying online calendering. The transparent tablets are matrix formulations with the drug dissolved in the matrix (amorphous solid dispersions). (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

The molten matrix exhibits a high density and can deliver tablets of reduced size (Fig. 2). Drug loads of more than 70% have been obtained for controlled-release products. The first product approved was a verapamil HCl 240 mg sustained-release formulation bioequivalent to Knoll's Isoptin® RR (Fig. 3), a major step to further developments in tailoring controlled-release profiles. An in vitro–in vivo correlation (IVIVC)—level A—for verapamil HCl 240 mg SR Meltrex tablets was developed and published [17].

Highly soluble drugs such as metoprolol tartrate are often absorbed too quickly to achieve the desired sustained release. The extrudate of the β_1-adrenergic antagonist should achieve the same in vitro (constant, linear release) and in vivo characteristics (AUC, C_{max}) as the innovator product (Beloc-Zok®) by the use of a different salt of metoprolol as starting material (tartrate instead of succinate) and different formulation principle (monolithic molten matrix instead of multiparticulate system [18,19]. The results demonstrate that Meltrex is capable of sustaining the release of metoprolol to match a given in vivo profile. Moreover, as shown in this case, it was even possible to start from different salts of the free base and still obtain the desired concentration/time profile of the active. Meltrex matched the profile of a significantly different formulation principle, namely, a multiparticulate system as used in the Beloc-Zok. Again a level A IVIVC was developed (Fig. 4).

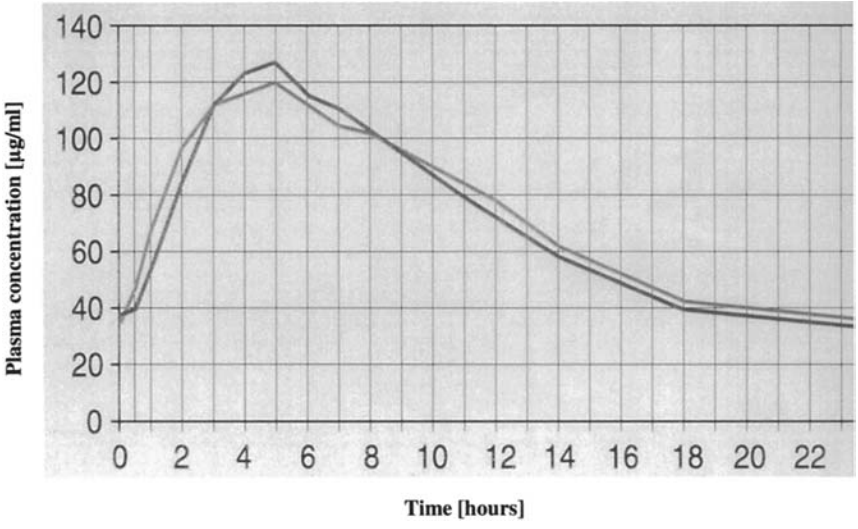


Figure 3 Synoptic plot of geometric mean concentrations of verapamil HCl, $n = 24$ healthy volunteers, steady state, multiple dose. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

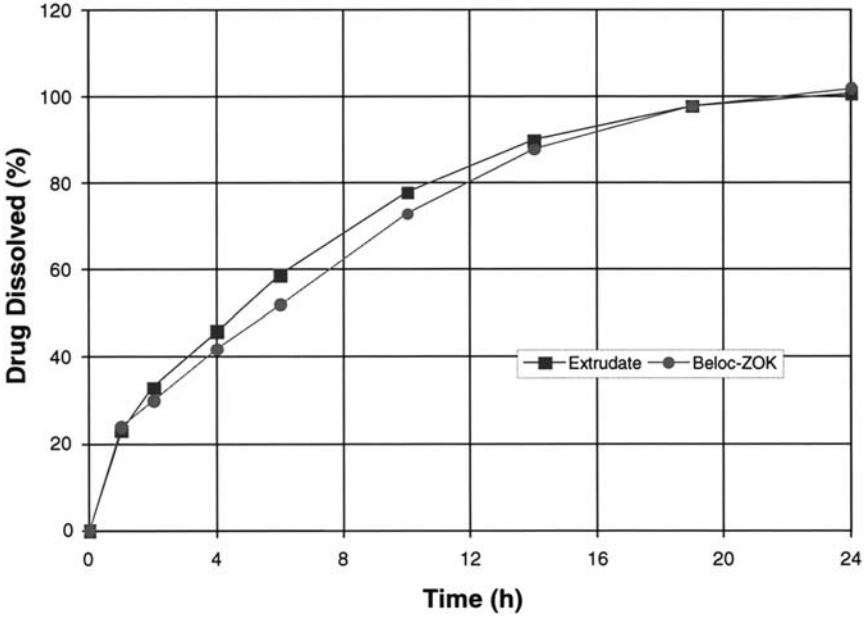


Figure 4 Metoprolol tartrate 100-mg extrudate modified-release tablet ($n = 6$) versus metoprolol succinate 95 mg (Beloc-Zok retard tablet = 100 mg tartrate, reference). The in vitro drug release was tested according to the USP 23 method, e.g., paddle apparatus, 100 rpm; simulated intestinal fluid pH 6.8, no change, 24 h. (See color insert.)

A pilot study was conducted to compare the concentration time profiles of the reference Beloc-Zok and the Meltrex formulation after a single dose (Fig. 5). Within the limits of a small pilot study it can be concluded from these pharmacokinetic data that the two formulations, with different salts of metoprolol, do not differ in biological relevance under fasted conditions.

B. Solid Dispersions with Meltrex Technology

A number of solid dispersions have been developed using the melt extrusion process [20–22] with a drug load ranging from 30% up to 60% with real-time stability up to 9 years (Table 1).

Nevertheless, the formulation as a solid dispersion or in the amorphous state bears the intrinsic risk of reverting to the more stable crystalline form. To secure storage stability at elevated temperatures, compositions with glass transition temperatures significantly above the storage conditions would be preferable

Copyright © 2003 Marcel Dekker, Inc.

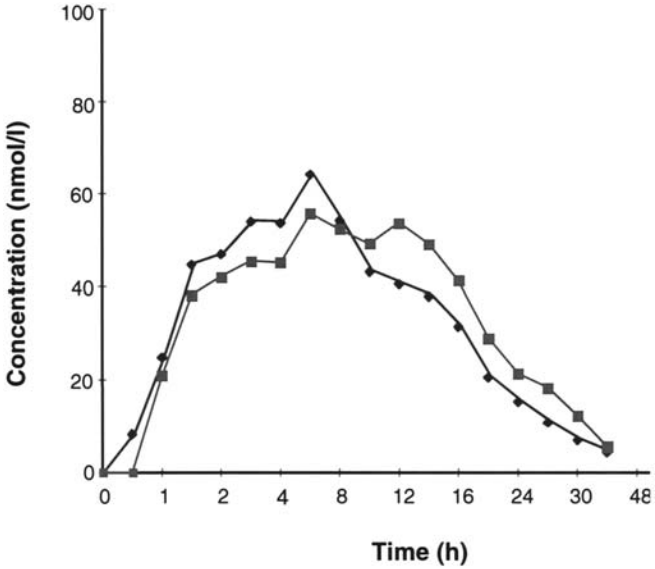


Figure 5 Synoptic plot of geometric mean concentrations of metoprolol (nmol/L) versus time (h). Squares: metoprolol tartrate 100-mg extrudate tablet; diamonds: metoprolol succinate 95-mg retard tablet (Beloc-Zok). (See color insert.)

in general. The fundamental question of under what conditions can reasonable certainty of the shelf-life stability of the pharmaceutical product be ensured needs to be addressed [23]. To be cautious, however, a whole range of specific analytical methods are currently applied to further prove the quality and stability of the solid dispersion Meltrex products (Table 2).

Table 1 Stability Data on Solid Solution Formulations Manufactured by Meltrex Process

Drug substance	Melting point (°C)	~Stable period proved to date (years)
Esuprone	115	9
Furosemide	206	5
Nifedipine	172–174	7
Paracetamol	169	4
LU 53439	125–130	6

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Analytical Methods Applied to Examine Solid Dispersions Manufactured by the Meltrex Process

Analytical method
Optical microscopy
Raman microscopy
X-ray diffraction
Thermal analysis
NIR
Microcalorimetry

V. REGULATORY ISSUES

Products from the Meltrex process have been approved in major European countries. It was found that the process technology lends itself to comprehensive documentation, thus satisfying regulatory authorities. It is a major advantage that extrusion is a mature engineering technology. As a process it provides many parameters, such as feeding rate, segmental temperatures, and pressure or applied vacuum, which can be monitored online with local meters and sensors. Such data contribute to the comprehensive documentation and the quality of production lots and may finally simplify quality control. Meltrex components, specifically designed for pharmaceutical use, and good manufacturing practice facilities dedicated to the production of clinical samples have been available for several years.

VI. TECHNOLOGY POSITION

The established part of the technology, including the elaborate know-how for ingredient composition, will be used for forthcoming pharmaceutical developments. A sound base of intellectual property rights for Meltrex technology has been built up, covering both the equipment and formulations. It is our strategy to carry out contract development and manufacture for third parties. Therefore, high-volume capacities have now been installed and are already in operation for production.

Copyright © 2003 Marcel Dekker, Inc.

VII. FUTURE DIRECTIONS

A particularly strong relationship exists between polymer chemistry and drug delivery, since most drug delivery systems depend on polymeric materials. Meltrex combines the use of polymers and their intrinsic properties with a convenient process leading to a widespread field of applications. The application of solid dispersion techniques in the research, development, and production of controlled-release pharmaceuticals is gaining increased attention. The Meltrex technology enables users to benefit from:

Fine-tuned pharmacokinetic profiles up to zero-order kinetics.
Improved bioavailability.
Circumvention of problems associated with polymorphism.

Thus Meltrex technology is a profitable strategic tool from drug rescue through prevention of generic erosion.

REFERENCES

1. WL Chiou, S Riegelman. Pharmaceutical application of solid dispersion systems. J Pharm Sci 60:1281–1302, 1971.
2. J Ford. The current status of solid dispersions. Pharm Acta Helv 61:69–88, 1986.
3. H Nogami, T Nagai, A Kondo. Dissolution kinetics of poly vinyl pyrrolidone. Chem Pharm Bull 18:1185–1187, 1970.
4. C Vervaet, L Baert, JP Remon. Extrusion-spheronisation—a literature review. Int J Pharm 116:131–146, 1995.
5. N Follonier, E Doelker, ET Cole. Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials. J Control Rel 36:243–250, 1995.
6. N Follonier, E Doelker, ET Cole. Evaluation of Hot-Melt-Extrusion as new technique for the production of polymer based pellets for sustained release capsules containing high loadings of freely soluble drugs. Drug Dev Ind Pharm 20:1323–1339, 1994.
7. M Adel El-Egakey, M Soliva, P Speiser. Hot extruded dosage forms. Pharm Acta Helv 46:31–52, 1971.
8. T Ozeki, H Yuasa, Y Kanaya. Application of the solid dispersion method to the controlled release medicine. IX. Difference in the release of flurbiprofen from solid dispersions with poly(ethylene oxide) and hydroxypropylcellulose and the interaction between medicine and polymers. Int J Pharm 155:209–217, 1997.
9. MA Khan, AH Shojaei, AA Karnachi, IK Reddy. Comparative evaluation of controlled-release solid oral dosage forms prepared with solid dispersions and coprecipitates. Pharm Technol 5:58–72, 1999.

Copyright © 2003 Marcel Dekker, Inc.

10. V Tantishaiyakul, N Kaewnopparat, S Ingkatawornwong. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. Int J Pharm 181:143–151, 1999.
11. G Zingone, M Moneghini, P Rupena, D Vojnovic. Characterization and dissolution study of solid dispersions of theophylline and indomethacin with PVP/VA copolymers. STP Pharma Sci 2:186–192, 1992.
12. N Follonier, E Doelker, ET Cole. Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials. J Control Rel 36:243–250, 1995.
13. K Yano, A Kajiyama, M Hamada, K Yamamoto. Constitution of colloidal particles formed from a solid dispersion system. Chem Pharm Bull 45:1339–1344, 1997.
14. A Abd, A El-Bary, AS Geneidi, SY Amin, AA El-Ainan. Preparation and pharmacokinetic evaluation of carbamazepine controlled release solid dispersion granules. J Drug Res Egypt 22:15–31, 1998.
15. H-H Grünhagen. Polymer/drug-melt extrusion: therapeutic and technological appeal. Pharm Tech Eur 8:22–28, 1996.
16. K Nakamichi, H Yasuura, H Fukui, M Oka, S Izumi, T Andou, N Shimizu, K Ushimaru. A process for the manufacture of nifedipine hydroxypropyl–methylcellulose phthalate solid dispersions by means of a twin screw extruder and appraisal thereof. Yakuzaigaku 56:15–22, 1996.
17. J Breitenbach, A Lassmann, J Neumann, J Noertersheuser, J Rosenberg, D Schoebel, C Vollgraf, J Zeidler. Development of an in vitro–in vivo correlation—level A—for a verapamil-HCL SR formulation prepared by melt-extrusion technology. American Association of Pharmaceutical Scientists, Annual Meeting Abstracts, San Francisco, 1999 (abstract 456).
18. J Breitenbach, S Koehne, M Mägerlein, J Neumann, U Reinhold, C Vollgraf, J Zeidler. Development of an in vitro–in vivo correlation for a metoprolol-tartrate modified release formulation prepared by melt extrusion technology. Proc Int Symp Control Rel Bioact Mater 27:443–444, 2000.
19. J Breitenbach, B Liepold, M Mägerlein, J Neumann, U Reinhold, J Rosenberg, C Vollgraf, J Zeidler. Modified release metoprolol tablets by melt extrusion and online calendering. Proc Int Symp Control Rel Bioact Mater 26:941–942, 1999.
20. J Breitenbach, W Schrof, J Neumann. Confocal raman spectroscopy: analytical approach to solid dispersions and mapping of drugs. Pharm Res 16:1109–1113, 1999.
21. G Berndl, J Breitenbach, J Neumann, U Reinhold, J Rosenberg, C Vollgraf, J Zeidler. Polymer/drug-melt extrusion: control of drug release and morphology in pharmaceutical formulations. American Association of Pharmaceutical Scientists. Annual Meeting Abstracts, San Francisco, 1998, pp. 296.
22. J Breitenbach, G Berndl, J Neumann, J Rosenberg, D Simon, J Zeidler. Solid dispersions by an integrated melt extrusion system. Proc Int Symp Control Rel Bioact Mater 25:804–805, 1998.
23. C Hancok, SL Shamblin, G Zografi. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. Pharm Res 12:799–805, 1995.

Copyright © 2003 Marcel Dekker, Inc.

12

DissoCubes—A Novel Formulation for Poorly Soluble and Poorly Bioavailable Drugs

Rainer H. Müller, Claudia Jacobs, and Oliver Kayser
Free University of Berlin, Berlin, Germany

I. INTRODUCTION

About 10% of the drugs developed by now are poorly soluble and have bioavailability problems; estimates for the future predict that about 40% of the newly developed drugs will be poorly soluble and subsequently show problems for reaching a therapeutically relevant blood level. Therefore, there is an urgent need to find solutions for the formulation of these poorly soluble drugs. Preferably, such a new formulation principle should be applicable to almost any poorly soluble drug, independent of its chemical structure and spatial molecular dimensions.

A simple approach to improve the bioavailability of orally administered drugs is micronization. However, especially for drugs with a low saturation solubility, the achieved increase in dissolution velocity might not lead to sufficiently high blood levels. Therefore, alternative formulation techniques to existing approaches [1,2] need to be developed.

To achieve a broadly applicable technology, increasing interest has been focused on drug nanoparticles in the last few years. Going beyond micronization leads to a further increase in the dissolution velocity due to an even larger surface area. Examples of this are the so-called Hydrosols® developed by Sucker [3–6] and NanoCrystals® offered by NanoSystems, a division of Elan Pharmaceutical Technologies [7–9]. An additional effect can be achieved by a controlled structural change in drug nanoparticles, which means reducing the crystallinity and

Copyright © 2003 Marcel Dekker, Inc.

increasing the amorphous fraction. Examples of drug nonoparticles with structural changes are the products NanoMorph™ marketed by Knoll/BASF Pharma (company brochure) and the drug nanosuspensions marketed under the name DissoCubes® [10,11]. DissoCubes combine the advantages of using a size reduction technique (i.e., NonoCrystals) with the advantages of a precipitation technique (i.e., Hydrosols®, NanoMorph™) opening the opportunity to induce structural changes, which means increasing the amorphous fraction [10,11].

II. HISTORICAL DEVELOPMENT

The technique for preparing hydrosols was developed by Sucker [3–6] based on the traditional "via humida paratum" for ointments, DAB 6 [12]. For long-term stabilization, lyophilization of the drug nanoparticle suspension is recommended [3]. A significant limitation of this method is the need for the drug to be soluble in at least one solvent and, simultaneously, that this solvent be miscible with a nonsolvent. However, many newly developed drugs are simultaneously poorly soluble in aqueous and organic media, thus excluding use of the precipitation technique.

Jet milling leads to powders with lowest mean diameters of around 3–5 μm. The size distribution ranges from approximately a few hundred nanometers to about 25 μm and the total fraction of nanoparticles is extremely low [13]. Ball or pearl mills can create suspensions with the majority of particles being in the nanometer range. However, problems associated with these mills are long milling times, up to almost 1 week, and erosion from the pearls contaminating the product [14].

The task was therefore to use a technique for size reduction, providing the required features for an industrial process [e.g., simple, cost-effective, no or low product contamination with heavy metals (below 10 ppm), and simultaneously open features to change the structure of particles as is possible in a precipitation process]. This was realized by developing the DissoCubes technology, which means production of a suspension of drug nanoparticles (nanosuspension) by high-pressure homogenization [10,11,13,15].

III. DESCRIPTION OF THE DISSOCUBES TECHNOLOGY

A. Production Technique for DissoCubes

The preparation process for DissoCubes nanosuspensions is very simple. The powered drug is dispersed in an aqueous surfactant or polymer solution to yield a traditional macrosuspension. The dispersion is performed by high-speed stirring, for example using a Silverson homogenizer or an ultraturrax stirrer. The

Copyright © 2003 Marcel Dekker, Inc.

obtained so-called "presuspension" is then high-pressure-homogenized using a piston-gap homogenizer, for example APV Gaulin machines (APV Homogenizer Deutschland GmbH, Lübeck/Germany). Typical pressures applied are between 500 and 1500 bar; in general a minimum of five homogenization cycles and a maximum of 15–20 cycles is required.

High-pressure homogenization leads to a very fine product even allowing intravenous administration. Intravenous particulate products require a very low content of particles in the range of a few micrometers to avoid blocking of the capillaries. In general, nanosuspensions of DissoCubes contain fewer particles larger than 5 μm than emulsions for parenteral nutrition [16,17]. For oral administration, the content of particles the size of a few micrometers is less critical. However, it should be very low to benefit from the special features of drug nanoparticles, increased dissolution velocity but—even more important—increased saturation solubility. The effect of an increase in saturation solubility is only pronounced below a particle size of approximately 1–2 μm [18,19]; therefore, the content of drug microparticles should be minimized to fully benefit from the nanosuspension properties.

A suitable laboratory scale homogenizer is the Micron LAB 40 (APV Homogenizer Deutschland GmbH, Lübeck/Germany). Alternatively, Stansted homogenizers can be used [20] and have been successfully employed to process suspensions with a solid content of 40%. In addition, the Stansted homogenizers allow higher pressures, for example 3000 bar and above. A higher pressure reduces the required number of production cycles. It also leads to a smaller product because the maximum dispersitivity that can be reached is a function of the power density, the homogenization pressure [21].

B. Special Features of DissoCubes

Two general features of drug nanoparticles should be highlighted: (a) the increase in dissolution velocity and (b) the general adhesiveness of nanoparticles.

The increase in dissolution velocity is due to an increase in surface area going beyond that of micronized products. Fine powders/particles possess an increased adhesiveness very well known from powder technology. These features improve bioavailability. Much in vivo data generated with drug nanoparticles by NanoSystems confirm this [22].

However, there are two more interesting features of drug nanoparticles (i.e., DissoCubes): (a) an increase in saturation solubility and (b) structural changes inside the particles. The latter depends very much on the means of production (e.g., introduction of high energy to increase the amorphous fraction as performed by high-pressure homogenization).

The Kelvin equation describes the increase in vapor pressure as a function of the curvature of liquid droplets [23]:

Copyright © 2003 Marcel Dekker, Inc.

$$\ln \frac{P_r}{P_\infty} = \frac{2\,\gamma V_m}{rRT} \quad (1)$$

where P_r = vapor/dissolution pressure with particle radius r; P_∞ = vapor/dissolution pressure with infinite particle size; γ = interfacial tension; V_m = molar volume; R = gas constant; T = absolute temperature; r = particle radius.

The situation of increased vapor pressure at a liquid/gas interface is comparable to the dissolution pressure at a solid/liquid interface, which means the dissolution pressure occurring at the surface of drug particles. Reducing the particle size below the size threshold of 1–2 μm leads to a distinct increase in the dissolution pressure, thus shifting the solubility equilibrium toward an increased saturation solubility. The dependency of the saturation solubility on the particle size is also contained in the Ostwald-Freundlich equation. The dissolution velocity is further enhanced due to a decrease in the diffusional distance at very small particle size as being described in the Prandtl equation [19]. That means there are three parameters affected that lead to an increase in the dissolution velocity according to the Noyes-Whitney equation (i.e., surface area, A, saturation solubility, c_s, and diffusional distance, h). The effects of increased dissolution pressure and increased concentration gradient $(c_s - c_x)/h$ leading to an increased dissolution velocity are summarized in Figure 1 [24].

For RMKP22, a drug against multidrug resistance (MDR) of tumor cells, an increase in the saturation solubility by a factor of 2 was found [25]. Considering this increase in saturation solubility related to the size in the nanometer range, it is desirable to keep the contamination of microparticles as low as possible even for oral administration.

An additional very important feature is a potential change in the structure of the drug nanoparticles, which means an increasing amount of the amorphous fraction. It is also known from the literature that amorphous drugs possess a higher saturation solubility than their crystalline counterparts, a classic example being griseofulvin [26,27]. This is exploited in the drug nanoparticle technology by Knoll/BASF Pharma using special precipitation conditions and marketed as the product called NanoMorph™. Instead of using precipitation with all its limitations (see below), transformation from the crystalline status to an amorphous product can also be obtained by high-energy input, known from tabletting technology reporting about the transformation of a low-energy modification to higher-energy modifications under tabletting pressure [28]. High-pressure homogenization is a high-energy process; the drug particles are exposed to a power density of up to 10^{13} Watt/m^3, a density comparable to power densities observed in nuclear power stations. This high energy breaks down the microparticles to nanoparticles and can also induce the change to an increased amorphous fraction or completely amorphous particles [29,30]. Figure 2 shows the X-ray diffractogram of the drug RMKP22 before processing and after changing the drug to an amorphous nanosuspension.

Copyright © 2003 Marcel Dekker, Inc.

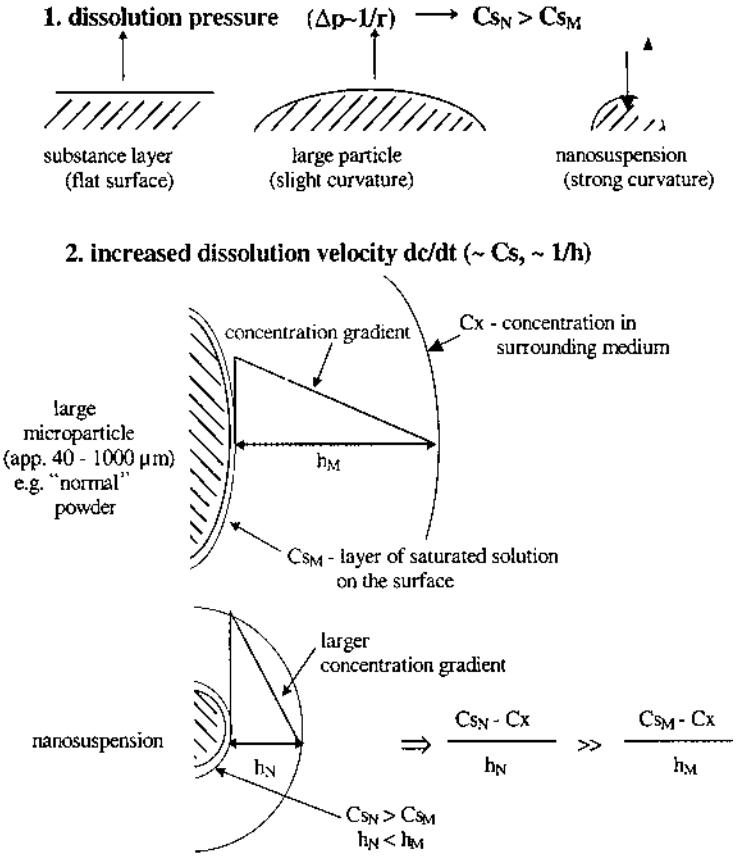

1. dissolution pressure (Δp~1/r) ⟶ $Cs_N > Cs_M$
substance layer (flat surface)
large particle (slight curvature)
nanosuspension (strong curvature)
2. increased dissolution velocity dc/dt (~ Cs, ~ 1/h)
concentration gradient
Cx - concentration in surrounding medium
large microparticle (app. 40 - 1000 µm) e.g. "normal" powder
h_M
Cs_M - layer of saturated solution on the surface
larger concentration gradient
nanosuspension
h_N
$\frac{Cs_N - Cx}{h_N} >> \frac{Cs_M - Cx}{h_M}$
$Cs_N > Cs_M$
$h_N < h_M$

Figure 1 Increased dissolution pressure at stronger curvature of the surface (upper) and comparison of c_s, h, and resulting concentration gradient between a drug microparticle and a drug nanoparticle. (After Ref. 24 with permission.)

If the drug is very hard and requires high energy for transition, there will be no change in the crystalline structure or only an amorphous layer onto the surface; for other drugs complete transformation to an amorphous particle occurs (Fig. 3).

C. Release Properties of DissoCubes

A general problem with poorly soluble drugs is their low saturation solubility and related slow dissolution velocity. To achieve sufficiently high bioavailability, fast dissolution and an increase in saturation solubility are beneficial. Therefore,

Copyright © 2003 Marcel Dekker, Inc.

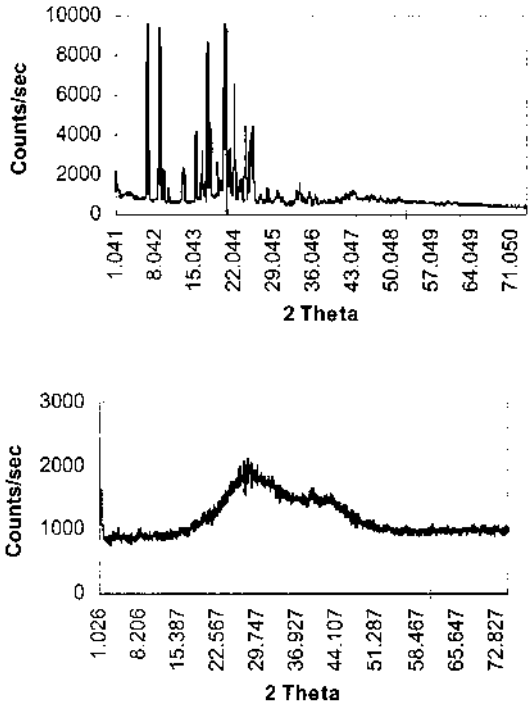


Figure 2 X-ray diffractogram of RMKP powder (upper) and of the RMKP22 nanosuspension (lower). (After Ref. 29 with permission.)

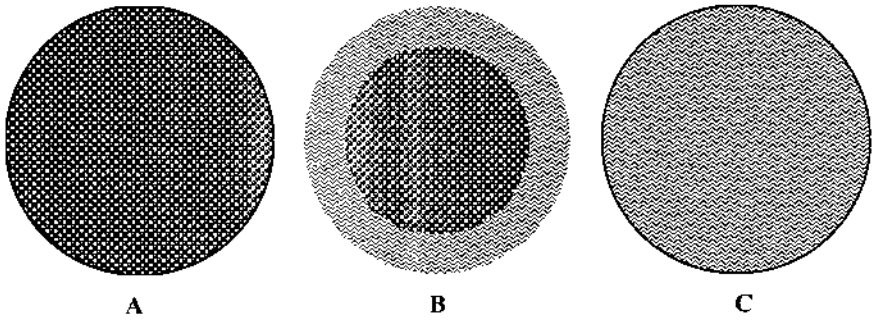


Figure 3 Drug nanoparticles of completely crystalline nature (A), amorphous layer onto the surface (B), and completely amorphous character (C).

Copyright © 2003 Marcel Dekker, Inc.

having a controlled release often is not the major point when applying a poorly soluble drug orally. Achieving a sufficiently high blood level is enough. That means the highest priority must be to create fast-dissolving drug nanoparticles with improved drug solubility. Prolonged release will occur anyway because, despite producing drug nanoparticles, the dissolution process is still much lower than with a highly soluble drug. Fast disolution and increased saturation solubility are special features of DissoCubes as discussed above.

IV. RESEARCH AND DEVELOPMENT OF DISSOCUBES FORMULATIONS

A. Feasibility Studies

Many different drugs have been processed by high-pressure homogenization to produce DissoCubes. Up to now each drug investigated could be converted into a nanosuspension. Examples include RMKP22 [15], carbamazepin (unpublished data), bupravaquone [31], aphidicolin [32], cyclosporine [33], paclitaxel [34], RMBB98 [35], azodicarbonamide [35], and prednisolone [17].

Amphotericin B as a poorly soluble drug is also of high interest for oral administration. Systemic mycosis is currently treated by intravenous administration of the liposomal product AmBisome®, which is expensive. Amphotericin B nanosuspension was developed to investigate whether a sufficiently high blood level could be obtained after oral administration. Amphotericin B was dispersed in an aqueous solution containing Tween 80® (0.25% w/w), Pluronic F68® (0.25% w/w), and cholic acid sodium salt (0.04% w/w). This presuspension was homogenized at 1500 bar for up to 15 cycles. To determine the content of micrometer particles, the nanosuspension was also analyzed by laser diffractometry using a Coulter LS 230. The laser diffractometer gives a volume distribution, which means the distribution is extremely sensitive to a few very large particles. The diameters of 95% and 99% are suitable parameters for assessing minimization of the microparticulate content. Figure 4 shows the reduction of microparticle content as a function of cycle number.

B. Fabrication Technique for DissoCubes

The DissoCubes are produced by high-pressure homogenization, which means the product is an aqueous suspension. However, such an aqueous suspension is in some cases only the desired final formulation for the market. More convenient formulation forms for the patient are tablets, capsules, or coated tablets. A major advantage of DissoCubes technology is that it can be combined as a novel technology with traditional dosage forms. The nanosuspension itself can be used as granulation fluid for producing granules and, if desired, compressing it into tab-

Copyright © 2003 Marcel Dekker, Inc.

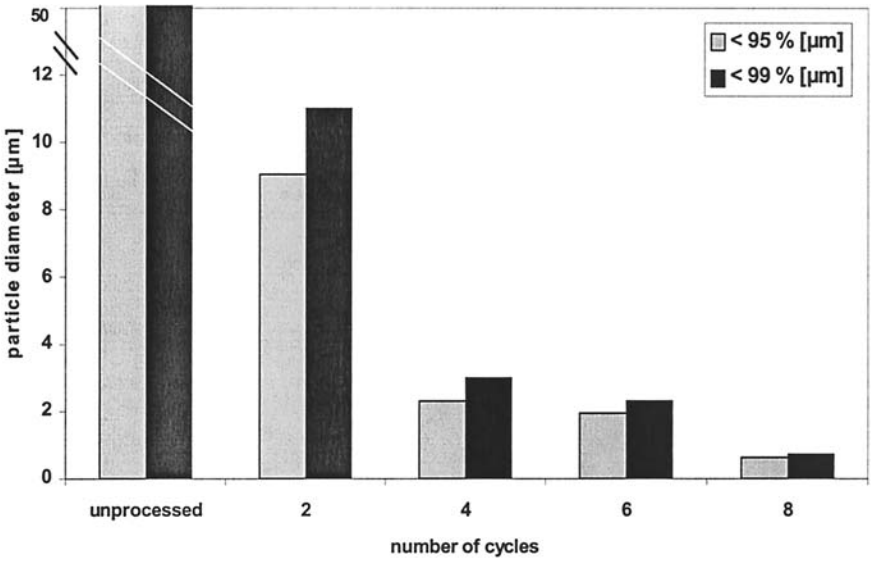


Figure 4 Diameters 95% and 99% of tarazepide nanosuspension as a function of homogenization cycles (laser diffractometry data) [20].

lets. Different ways of combining drug nanoparticles with traditional dosage forms have been described [22,36].

C. Scale-up Production of DissoCubes

High-pressure homogenization is a broadly used technique in different areas. Especially in the food area, large capacities of production are required, and high-capacity homogenizers are available. In the pharmaceutical industry, emulsions for parenteral nutrition are produced by high-pressure homogenization (e.g., Lipofundin®, Intralipid®). Typical batch sizes for these products are a few thousand kilograms.

DissoCubes technology requires a minimum of approximately five homogenization cycles to be run. A commercial homogenizer with a sufficiently high throughput is the Rannie 188 (about 2650 L/h, maximum pressure 1500 bar). The basic arrangement for large-scale production is to pass the batch several times through the same homogenizer in a feedback loop, which means the batch will go from product container 1 through the homogenizer to product container 2 and back and back and so on (Figure 5, upper diagram). To minimize production time it is recommended to place two homogenizers in series such that one passage

Copyright © 2003 Marcel Dekker, Inc.

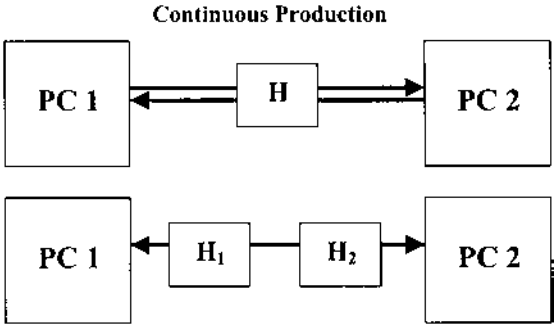


Figure 5 Production line for large-scale production of nanosuspensions being composed of product container PC (PC 1 and PC 2), and one (upper) or two homogenizers H (lower) for continuous production. In the lower setup one passage is equivalent to two homogenization cycles.

is equal to two homogenization cycles. This is possible because the equipment is off-the-shelf and therefore low-cost. Figure 5 (lower diagram) shows the diagram for such a production unit being composed of two product containers and two homogenizers. Even when assuming 10 homogenization cycles, a batch size of 1 ton (1000 kg) can be processed within approximately 4 h.

D. In Vitro Cell Culture Studies with DissoCubes

DissoCubes have been widely introduced in different in vitro cell assays including RAW macrophage cell line and peritoneal macrophages for cytotoxicity testing [32,37] and macrophages in infection models like leishmaniasis and tuberculosis. Among the drugs processed to DissoCubes and introduced in test assays, there were clinically used drugs, as mentioned earlier, as well as others of preclinical interest, such as a series of natural products (aurones, aphidicolin [32]) and semisynthetic naphthinazol-4,9-quinones [38].

Regarding toxicity, it is noteworthy that for the natural product aphidicolin the cytotoxic potential was reduced significantly by formulation as a nanosuspension [39]. In contrast to the dissolved drug, the number of mice treated with an aphidicolin nanosuspension showed fewer side effects and a lower mortality rate. Also, drug targeting effects were demonstrated for aphidicolin nanosuspensions in a RAW macrophage model indicating the potential of DissoCubes as a drug delivery system. The drug was efficiently taken up by these phagocytic cells [40], and a significant reduction in the EC_{50} from 0.42 to 0.003 μg/mL [39] for the incubation of aphidicolin nanosuspensions with *Leishmania*-infected macrophages could be demonstrated. By this simple example, it could be shown that

Copyright © 2003 Marcel Dekker, Inc.

using DissoCubes will be an interesting drug delivery system for infectious diseases such as leishmaniasis or tuberculosis, where macrophages as host cells are involved.

E. In Vivo Studies with DissoCubes

Extensive in vivo studies have been performed with NanoCrystals® produced by pearl milling. These in vivo data are generally valid for all drug nanoparticles independent of the manner of production and are in general very impressive. There will be an additional benefit if the drug nanoparticles have special features, for example being amorphous as shown for NanoMorph™ (company Knoll/BASF) or showing structural changes like DissoCubes [41]. The benefits of drug nanoparticles for oral administration were nicely summarized by Liversidge in his presentation at the CRS Annual Meeting in Kyoto [22].

Drug nanoparticles (both human and animal data) (a) improve bioavailability, (b) improve dose proportionality, (c) reduce fed/fasted variability, (d) reduce intersubject variability, and (e) enhance the absorption rate.

As an example for DissoCubes, data of orally administered amphotericin B are shown in Figure 6. There is a high interest in finding an oral delivery system for amphotericin B to circumvent parenteral administration. Amphotericin B has been processed as described above and was given to *Leishmania*-infected mice by gavage inoculation. In contrast to approved and commercially available

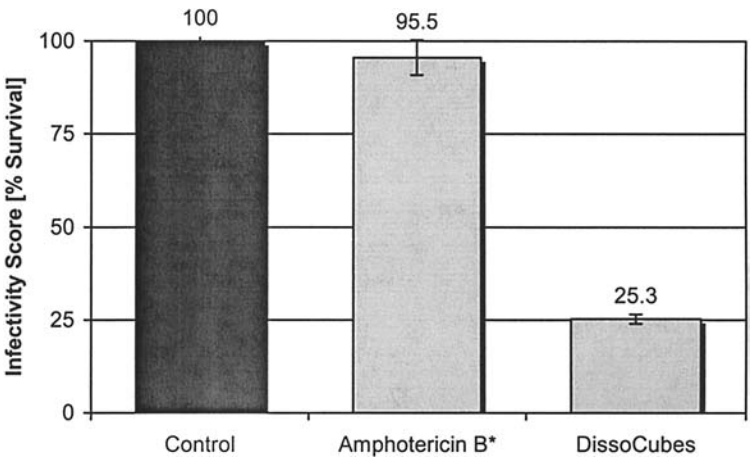


Figure 6 Infectivity score as percentage survival of parasites after oral administration of amphotericin B as a micronized powder and DissoCubes.

Copyright © 2003 Marcel Dekker, Inc.

drug formulations for the treatment of GIT mycosis, amphothericin B is not, or is only to a minor extent, absorbed after oral administration. Formulating this drug as DissoCubes and giving it orally, the number of *L. donovani* parasites in vivo—a parameter for the rate of gastrointestinal uptake—was reduced significantly. In contrast to the commercial crude amphotericin B (micronized drug particles) that was tested in parallel as a reference control, the infectivity score was reduced to 25% and 95%, respectively, as depicted in Figure 6 [40].

V. REGULATORY ISSUES

From the regulatory point of view, the introduction of a new product has two aspects: the regulatory issues concerning the production line itself and finally the product. The production lines used for producing DissoCubes nanosuspensions are already in use for the production of emulsions for parenteral nutrition. They are accepted by the regulatory authorities and therefore a priori no major difficulties should occur. The production lines available are made of materials suitable for pharmaceutical production. The unit itself is able to be qualified and validated [42,43].

In addition, the product itself needs to fulfill the regulatory criteria, for example contamination from the production unit. Nanosuspensions were produced applying the hardest production conditions, 1500 bar and 20 homogenization cycles. The dominant material in the steel is iron; therefore, the suspensions were analyzed regarding their iron content using atomic absorption spectroscopy (AAS). The iron content was below 1 ppm, in the acceptable range [44]. In addition, the homogenizers are handy for industrial purposes. They can be cleaned in place and sterilized in place by streaming steam.

VI. TECHNOLOGY POSITION AND COMPETITIVE ADVANTAGES

The hydrosol technology developed by Sucker and the NanoMorph™ system marketed by Knoll/BASF Pharma are both precipitation techniques. They require that the drug is soluble in at least one solvent and simultaneously that this solvent is miscible with a nonsolvent. This restricts a priori the general applicability of these techniques. In addition, many of the newly developed drugs are simultaneously insoluble in aqueous and organic media.

A much easier approach is producing nanoparticles by a deaggregation technique, which means a milling process. Competing technologies for DissoCubes are NanoCrystals by NanoSystems and the IDD technology by RTP in Canada. NanoSystems uses pearl milling to obtain drug nanoparticles. Basic

Copyright © 2003 Marcel Dekker, Inc.

problems from our point of view are erosion from the pearls and microbiological problems. According to Liversidge, milling times up to several days can be required [22]. It was reported by Buchmann et al. that longer milling times lead to erosion from balls [14], which means contamination of the product. In addition, milling over a few days might promote growth of germs in the suspensions; this will be especially a problem when producing sterile parenteral products.

An alternative method used by RTP in Canada is disintegration of the drug by microfluidization. The technology is based on the patents by D. H. Haynes [45,46], e.g., using a microfluidizer for particle milling. However, for use of a microfluidizer a higher number of cycles was reported to be required, e.g., up to 100 [47]. Considering the high number of passages for many drugs, this technology appears to have limited feasibility for an industrial production process.

VII. FUTURE DIRECTIONS AND PERSPECTIVES

To sum up, the production of drug nanoparticles is a universal technology to overcome the problems encountered with poorly soluble drugs, especially drugs that are simultaneously poorly soluble in aqueous and organic media. In contrast to other specialized approaches such as solubilization, complexation, and inclusion, the technique of forming drug nanoparticles can be applied universally to any drug.

Industrial, regulatory, and commercial market issues need to be considered. Comparing DissoCubes technology to precipitation techniques it has clearly distinct advantages. Comparing DissoCubes technology to other milling processes, from our point of view it has benefits regarding potential product contamination and especially regarding the feasibility to be introduced as an industrial large-scale production process.

An essential prerequisite for the market is the exclusiveness of the product. This is given by the worldwide PCT application for the DissoCubes nanosuspension technology and the US patent issued in 1999.

REFERENCES

1. KH Bauer, KH Frömming, C Führer. Lehrbuch der Pharmazeutische Technologie. 6th ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH, 1999.
2. KH Frömming. Cyclodextrine—eine vielseitig verwendbare Gruppe neuer Hilfsstoffe. In: RH Müller, GE Hildebrand, eds. Pharmazeutische Technologie: Moderne Arzneiformen. 2nd ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH, 1998, pp. 13–17.
3. H Sucker. Hydrosole, eine Alternative für die parenterale Anwendung von schwer

Copyright © 2003 Marcel Dekker, Inc.

wasserlöslichen Wirkstoffen. In: RH Müller, GE Hildebrand, eds. Pharmazeutische Technologie: Moderne Arzneiformen. 2nd ed. Stuttgart: Wissenschaftliche Verlags Gesellschaft, 1998, pp. 383–391.
4. M List, H Sucker. Pharmaceutical colloidal hydrosols for injection. GB patent 2200048, 1992.
5. P Gaßmann, H Sucker. Improvements in pharmaceutical compositions. GB patent 2269536, 1994.
6. P Gaßmann, M List, A Schweitzer, H Sucker. Hydrosols—alternatives for the parenteral application of poorly water soluble drugs. Eur J Pharm Biopharm 40:64–72, 1994.
7. GG Liversidge, KC Cundy. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs. I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm 125:91–97, 1995.
8. GG Liversidge, P Conzentino. Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. Int J Pharm 125:309–313, 1995.
9. GG Liversidge, K Cundy, JF Bishop, DA Czekai. Surface modified drug nanoparticles. US patent 5,145,684, 1992.
10. RH Müller, R Becker, B Kruss, K Peters. Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of dissolution. US patent 5,858,410, 1999.
11. RH Müller. Nanosuspensionen—eine neue Formulierung für schwerlösliche Arzneistoffe. In: RH Müller, GE Hildebrand, eds. Pharmazeutische Technologie: Moderne Arzneiformen. 2nd ed. Stuttgart: Wissenschaftliche Verlags Gesellschaft, 1998, pp. 393–399.
12. German Pharmacopoea DAB 6, 1926, p. 347.
13. RH Müller, K Peters, R Becker, BN Kruss. Nanosuspensions—a novel formulation for the i.v. administration of poorly soluble drugs. Proceedings of the 1st World Meeting of the Association de Pharmacie Galenique Industriele/International Association for Pharmaceutical Technology, Budapest, 1995, pp. 491–492.
14. S Buchmann, W Fischli, FP Thiel, R Alex. Aqueous microsuspension, an alternative intravenous formulation for animal studies. Proceedings of the Annual Congress of the Association de Pharmacie Galenique Industriele/International Association for Pharmaceutical Technology, Mainz, 1994, pp. 124.
15. RH Müller, K Peters. Nanosuspensions for the formulation of poorly soluble drugs. I. Preparation by a size-reduction technique. Int J Pharm 160:229–237, 1998.
16. C Schwarz, W Mehnert, RH Müller. Influence of production parameters of solid lipid nanoparticles (SLN) on the suitability for intravenous injection. Eur J Pharm Biopharm 40:24, 1994.
17. K Peters. Nanosuspensionen—ein neues Formulierungprinzip für schwerlösliche Arzneistoffe. PhD dissertation, Freie Universität, Berlin, Germany, 1999.
18. C Nyström. Dissolution properties of soluble drugs: theoretical background and possibilities to improve the dissolution behavior. In: RH Müller, S Benita, B Böhm, eds. Emulsions and Nanosuspensions for the Formulation of Poorly Soluble Drugs. Stuttgart: Medpharm Scientific Publishers, 1998, pp. 143–147.
19. M Mosharraf, C Nyström. The effect of particle size and shape on the surface specific

Copyright © 2003 Marcel Dekker, Inc.

dissolution rate of micronized practically insoluble drugs. Int J Pharm 122:35–47, 1995.
20. C Jacobs. PhD dissertation, Freie Universität Berlin, Germany, in preparation.
21. S Jahnke. The theory of high-pressure homogenization. In: RH Müller, S Benita, B Böhm, eds. Emulsions and Nanosuspensions for the Formulation of Poorly Soluble Drugs. Stuttgart: Medpharm Scientific Publishers, 1998, pp. 177–200.
22. GG Liversidge. Presentation at the Workshop of Particulate Drug Delivery Systems. 23rd International. Symposium on Controlled Release of Bioactive Materials, Kyoto, 1996.
23. DJW Grant, HG Brittain. Solubility of pharmaceutical solids. In: HG Brittain, ed. Physical Characterization of Pharmaceutical Solids. New York: Marcel Dekker, 1995, pp. 321–386.
24. RH Müller, BHL Böhm. Nanosuspensions. In: RH Müller, S Benita, B Böhm, eds. Emulsions and Nanosuspensions for the Formulation of Poorly Soluble Drugs. Stuttgart: Medpharm Scientific Publishers, 1998, pp. 149–174.
25. RH Müller, R Becker, B Kruss, K Peters. 1994. Pharmazeutische nanosuspensionen zur arzneistoffapplikation als systeme mit erhöhter.
26. PH List. Arzneiformenlehre. 4th ed. Stuttgart: Wissenschaftliche Verlags Gesellschaft mbH, 1985.
27. H Ahmed, G Buckton, DA Rawlins. Crystallisation of partially amorphous griseofulvin in water vapour: determination of kinetic parameters using isothermal heat conduction microcalorimetry. Int J Pharm 167:139–145, 1998.
28. H Kala, U Haak, U Wenzel, G Zessin, P Pollandt. Zum kristallographischen verhalten verhalten des carbamazepins unter pressdruck. Pharmazie 42:524–527, 1987.
29. BHL Böhm, MJ Grau, GE Hildebrand, AF Thünemann, RH Müller. Preparation and physical properties of nanosuspensions (DissoCubes) of poorly soluble drugs. Proc Int Symp Control Rel Bioact Mater 25:956–957, 1998.
30. MJ Grau, RH Müller. Increase of dissolution velocity and solubility of poorly soluble drugs by formulation as nanosuspension. Proceedings of the 2nd World Meeting of the Association de Pharmacie Galenique Industriele/International Association for Pharmaceutical Technology, Paris, 1998, pp. 623–624.
31. C Jacobs. Determination of physical stability of bupravaquone nanosuspension for in vivo use. Proceedings of the 3rd World Meeting of the Association de Pharmacie Galenique Industriele/International Association for Pharmaceutical Technology, Berlin, 2000, pp. 415–416.
32. O Kayser. Formulation of the poorly unsoluble antiprotozoal aphidicolin as injectable by production as nanosuspension. In: D Burgess, PJ Stout, eds. Injectable Dispersed Systems: Formulation, Processing and Performance. 2000 (in press).
33. S Runge. Feste Lipidnanopartikel (SLN) als kolloidaler Arzneistoffträger für die orale Applikation von Ciclosporin A. PhD dissertation, Freie Universität, Berlin, Germany, 1998.
34. BHL Böhm. Herstellung und Charakterisierung von Nanosuspension als neue Arzneiform für Arzneistoff mit geringer Bioverfügbarkeit. PhD dissertation, Freie Universität, Berlin, Germany, 1999.
35. M Grau. Untersuchungen zur Lösungsgeschwindigkeit, Sättigungslöslichkeit und

Copyright © 2003 Marcel Dekker, Inc.

Stabilität von hochdispersen Arzneistoffsuspensionen. PhD dissertation, Freie Universität, Berlin, Germany, 1999.
36. RH Müller, BHL Böhm, MJ Grau. Nanosuspensions—Formulierungen für schwerlösliche arzneistoffe mit geringer Bioverfügbarkeit. II. Stabilität, biopharmazeutische aspekte, mögliche arzneiformen und zulassungsfragen. Pharm Ind 61:175–178, 1999.
37. N Schöler, K Krause, O Kayser, RH Müller, H Hahn, O Liesenfeld. In vitro efficacy of atovaquone nanosuspensions against *Toxoplasma gondii*. Proceedings of the 3rd World Meeting of the Association de Pharmacie Galenique Industriele/International Association for Pharmaceutical Technology, Berlin 2000, pp. 331–332.
38. O Kayser, AF Kiderlen, H Laatsch. Antiparasitäre Wirkung von N1-alkyierten 1,4-Naphthinazol-4,9-chinonen. German patent 100 20 812.6, 2000.
39. O Kayser. Nanosuspensions for the formulation of aphidicolin to improve drug targeting effects against *Leishmania* infected macrophages. Int J Pharm 196:253–256, 2000.
40. RH Müller, O Kayser, C Jacobs. Nanosuspensions as particular drug formulations in therapy. Adv Drug Del Rev (in press).
41. RH Müller, MJ Grau, GE Hildebrand. Increase of solubility of poorly soluble drugs by transfer to DissoCubes using high pressure homogenization. Proc Int Symp Control Rel Bioact Mater 26:112–113, 1999.
42. T Schneppe, RH Müller. Qualitätsmanagement und Validierung in der pharmazeutischen Praxis. Aulendorf: Editio Cantor Verlag, 1999, pp. 81–163.
43. RH Müller, S Gohla, A Dingler, T Schneppe. Large scale production of solid lipid nanoparticles (SLN) and nanosuspensions (DissoCubes). In: D Wise, ed. Handbook of Pharmaceutical Controlled Release Technology (in press).
44. KP Krause, O Kayser, K Mäder, R Gust, RH Müller. Heavy metal contamination of nanosuspensions produced by high-pressure homogenisation. Int J Pharm 196: 169–172, 2000.
45. DH Haynes. Phospholipid-coated microcrystals: injectable formulations of water-insoluble drugs. US patent 5,091,187 and 5,091,188, 1992.
46. DH Haynes. Microdroplets of water insoluble drugs and injectable formulations containing same. US patent 4,725,442, 1988.
47. A Dearn. Atovaquone pharmaceutical compositions. PCT International Publication WO 94/14426, 1994.

Copyright © 2003 Marcel Dekker, Inc.

13

IDD Technology: Oral Delivery of Water-Insoluble Drugs Using Phospholipid-Stabilized Microparticulate IDD Formulations

Awadhesh K. Mishra, Michael G. Vachon, Pol-Henri Guivarc'h, Robert A. Snow, and Gary W. Pace*
SkyePharma Canada Inc., Montreal, Quebec, Canada

I. INTRODUCTION

Drug insolubility is one of the most intractable problems in new drug development and in reformulation of existing medications. This chapter describes a novel approach, Insoluble Drug Delivery (IDD™) technology, which has successfully addressed the problem of water-insoluble drug delivery. Without intending a comprehensive review of the latter, this chapter briefly compares the attributes of the IDD approach and other formulation technologies for water-insoluble drugs. Example formulations employing IDD technology are discussed, particularly with respect to their ability to improve oral bioavailability.

Water-insoluble† drugs pose intricate problems in their formulation and delivery. Water insolubility of many drugs is often manifested in poor gastrointestinal absorption and bioavailability, intra- and interindividual bioavailability variations, and food interaction in their absorption after oral administration [1–3]. Some of the emerging oral drug delivery systems that have addressed the drug-insolubility problems are summarized in Table 1 [4–31].

Poorly water-soluble drugs traditionally have been formulated for oral administration through their micronization by air-jet milling [4]. Micronization in-

* Current affiliation: QRx Pharma Inc., Winchester, Massachusetts, U.S.A.
† In this chapter the term "water-insoluble" also includes poorly or sparingly water-soluble drugs.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Some Emerging Oral Drug Delivery Systems for Water-Insoluble or Poorly Water-Soluble Drugs

Formulation technology	Characteristics
Micronization	
Traditional micronization [4,5]	Particle size reduction, typically with an air-jet mill. Dissolution rate enhancement via increased surface area. High drug payload. Bioavailability improvement.
Surface-stabilized small particle technology	
Insoluble Drug Delivery (IDD) technology [6–11]	Surface stabilized submicrometer size particles with biocompatible and safe phospholipids and other surface modifiers. Enhancement of dissolution rate via increased surface area. High drug payload. Bioavailability improvement. Uses GRAS-listed traditional excipients.
NanoCrystal technology [12–14]	Surface stabilized particles of ca. 400 nm. Dissolution rate enhancement via increased surface area. High drug payload. Bioavailability improvement.
Nanosuspensions [15]	Surface stabilized particles of submicrometer size. Dissolution rate enhancement via increased surface area and increased saturation solubility. Bioavailability improvement.
Matrix inclusion technology	
Nanospheres and microspheres [16–18]	Submicrometer to micrometer size particles of biodegradable polymeric matrix with entrapped drug. Drug loading and release depend on solubility of the drug in polymeric matrix material.

Copyright © 2003 Marcel Dekker, Inc.

Nanosol technology [19]	Collagen- or gelatin-based drug matrices, 150–250-nm particles containing insoluble drugs.
Egalet CR system [20]	Dispersion of drug in water-degradable polymer matrix. Capable of sustained delivery via oral as well as long-term delivery into urinary bladder or vagina.
INDAS: insoluble drug absorption system [21]	Stabilized amorphous form of drug displays improved dissolution rate and absorption.
Hydrophobic carrier systems	
Solid lipid nanoparticles (SLN) [22], and emulsions [23]	High-pressure emulsification of drug dissolved in melted lipid followed by cooling to form solid particles with drug in the core or associated on the particle surface. Special case of oil-in-water (O/W) emulsion where the oil carrier is solid at ambient temperature. Restricted by low drug loading. O/W emulsions of liquid drug of lipophilic drug dissolved in oil are not very pragmatic for oral delivery because large-volume administration is required.
Liposomes [24]	Lipophilic drugs can be incorporated in the bilayers of liposomes. Very low drug loading. Limited mainly to parenteral and topical administration. Possible vehicle for oral vaccines.
Self-dispersible systems	
Self emulsifying or microemulsifying drug-delivery systems [25–27]	Active ingredient(s) dissolved in a carrier system of a lipophilic phase, surfactant and cosurfactant, and a hydrophilic phase. On mixing with gastric fluid makes O/W type emulsion or microemulsion giving rise to higher bioavailability. Restricted by the solubility of the drug in the vehicle and dispersibility in gastric fluid.

Copyright © 2003 Marcel Dekker, Inc.

creases their in vivo dissolution rates by reducing particle size and increasing surface area with a concomitant gain in bioavailability [4,5]. New approaches in formulating poorly soluble drugs, such as the use of surface stabilized nano- or microparticles* [6–15], inclusion in polymer or lipophilic matrices such as nanospheres* [16–21], hydrophobic carrier systems [22–24], self-dispersible systems [25–29], and molecular complexation with agents suitable for lipophilic drugs [30,31], have demonstrated significant improvements. Each technique, although displaying specific advantages, has characteristic limitations narrowing its suitability to only certain types of drugs. For instance, hydrophobic carrier systems or self-dispersible systems can be employed only for those drugs that are sufficiently soluble in the carrier. Similarly, a matrix-inclusion system can be employed if the extent of drug loading and the drug release profile within the gastrointestinal tract are acceptable.

While molecular complexes with hydrophilic carriers for water-insoluble drug delivery are well developed, e.g., cyclodextrin complexes [30], water-dispersible molecular aggregates, such as micelles and liposomes, provide interesting, albeit largely unexplored, alternatives. Transport of liposomes or other colloidal particulate systems via paracellular and transcellular routes from normal epithelial tissue or Peyer's patches leads to different outcomes of drug delivery and immunization, respectively [24,32]. Formulating water-insoluble drugs with polymerized, microencapsulated, polymer-coated, or targeted liposomes, together with a greater understanding of their cellular processing, will ultimately lead to effective therapies from oral liposomes [24].

Lipophilic drugs are harbored into liposomal bilayers with very low drug: vehicle ratios [10,11], thus limiting their utility only to high-potency insoluble drugs of vaccines.

A phospholipid-based drug delivery system for water-insoluble drugs, termed IDD [10,11] (formerly known as MicroDroplet [6,7] and MicroCrystal [8] technologies) is believed to be the first example to enable administration of highly concentrated drug substances as surface-modified microparticle formulations. Similar delivery systems exploiting these principles have been described subsequently [9,12–15]. Various IDD subtechnologies are described in Table 2. Previously reviewed IDD formulations for parenteral administration [10,11] include both IDD-P™, i.e., insoluble drug delivery of microparticle formulations, and IDD-D™, i.e., insoluble drug delivery as an aqueous dispersion of submicrometer-size droplets.

* Micro- or nanoparticles are defined as surface-stabilized submicrometer to micrometer size drug particles, and nanosphere represents submicrometer to micrometer size particles of a suitable solid matrix entrapped drug.

Copyright © 2003 Marcel Dekker, Inc.

Table 2 IDD Subtechnologies and Their Characteristics

IDD technology[a]	Characteristics	Administration route and examples
IDD-P™	Submicrometer-size particulate formulation stabilized with phospholipid with or without other surface modifiers. Steam-sterilized suspensions for parenteral administration. Can be γ-irradiated to sterilize in dry state. Applicable to broad range of drugs.	Oral (CTM650, cyclosporine) Parenteral (itraconazole, bupivacaine, and antineoplastic drugs: busulfan and 9-nitrocamptothecin) Inhalation (budesonide)
IDD-D™	Steam sterilized oil-in-water emulsion. Essentially pure water-insoluble liquid drug in the dispersed oil phase. Takes advantage of oil solubility of some water-insoluble solid drugs.	Parenteral (propofol, cyclosporine)
IDD-SE™ and IDD-ME™	Self-emulsifiable or self-microemulsifiable solution in a carrier containing lipophilic solvent and surfactant. Forms submicrometer-size emulsion or microemulsion on exposure to gastrointestinal environment. Takes advantage of drug solubility in oil and surfactant mixture.	Oral (CTM650, cyclosporine)
IDD-I™	Incorporates IDD-P particulate compositions within a biodegradable implantable carrier. Long-acting preparation of water-insoluble drugs. Applicable to a broad range of drugs.	Implantable (flurbiprofen, bupivacaine) Topical
IDD-O™	Micrometer to submicrometer-size particulate suspension of oil-insoluble drugs in a pharmaceutically active oily medium packaged within capsules or gelcaps. Site-specific delivery through enteric coating. Applicable to drugs that are insoluble in water and oil.	Oral (budesonide)

[a] These technologies are currently being applied to formulate a number of water-insoluble new chemical entities and to reformulate existing medicines (unpublished results).

Copyright © 2003 Marcel Dekker, Inc.

II. IDD-P FORMULATIONS

The IDD approach to insoluble drug delivery involves formulation of microparticles of water-insoluble drugs stabilized by surface-modifying agents such as phospholipids with or without other surface modifiers. Size reduction of drug particles dispersed in aqueous medium in the presence of phospholipids (and/or other surface modifiers) results in association of the latter with the newly cleaved plane of the freshly generated drug surface. In Figure 1, the electron micrographs display drug raw material as about 100 μm crystals, and an IDD-P formulation as about 0.5 μm surface-modified microparticles.

A. Structure

The use of phospholipids in the production of IDD formulations as multiphasic aqueous dispersions calls for a comparison between the IDD technology and liposomes. The distinctive feature is the presence of a hydrophilic core and phospholipid bilayers in liposomes versus a solid or liquid water-insoluble drug core and several phospholipid microstructural domains in the IDD particles (Fig. 2) [10]. The first phospholipid domain around the drug core of IDD particles consists of a surface-modifier primary layer. A second domain surrounding the drug core may include a few more phospholipid bilayers, small unilamellar vesicles, and/or other microstructures, e.g., micelles or mixed micelles. Microstructures of this domain may remain loosely associated with the stabilized drug core and move with the drug particle, giving rise to the observed hydrodynamic radii of the IDD particles. A third domain consists of small unilamellar vesicles and/or other microstructures <50 nm in diameter that are not associated with the drug core and move freely in the aqueous medium. It is believed that almost all of the drug material is sequestered within the first domain. Equilibrium partitioning of a relatively small amount of drug into the microstructures of the second and third domains is also possible [10].

B. Drug-Vehicle Interaction

The association of phospholipid molecules with the drug surface originates primarily from weak interactions such as hydrophobic, van der Waals, dipolar, or combinations thereof. Minimal (if any) chemical interaction exists between the phospholipid sheath and the drug core. A phospholipid palisade structure has been illustrated by determinations of phase transition temperatures typical of the phospholipid structures in IDD formulations [33]. Absence of strong interaction between the phospholipids and the drug entities in these formulations was also illustrated by ^{19}F-NMR chemical shift experiments [34].

Copyright © 2003 Marcel Dekker, Inc.

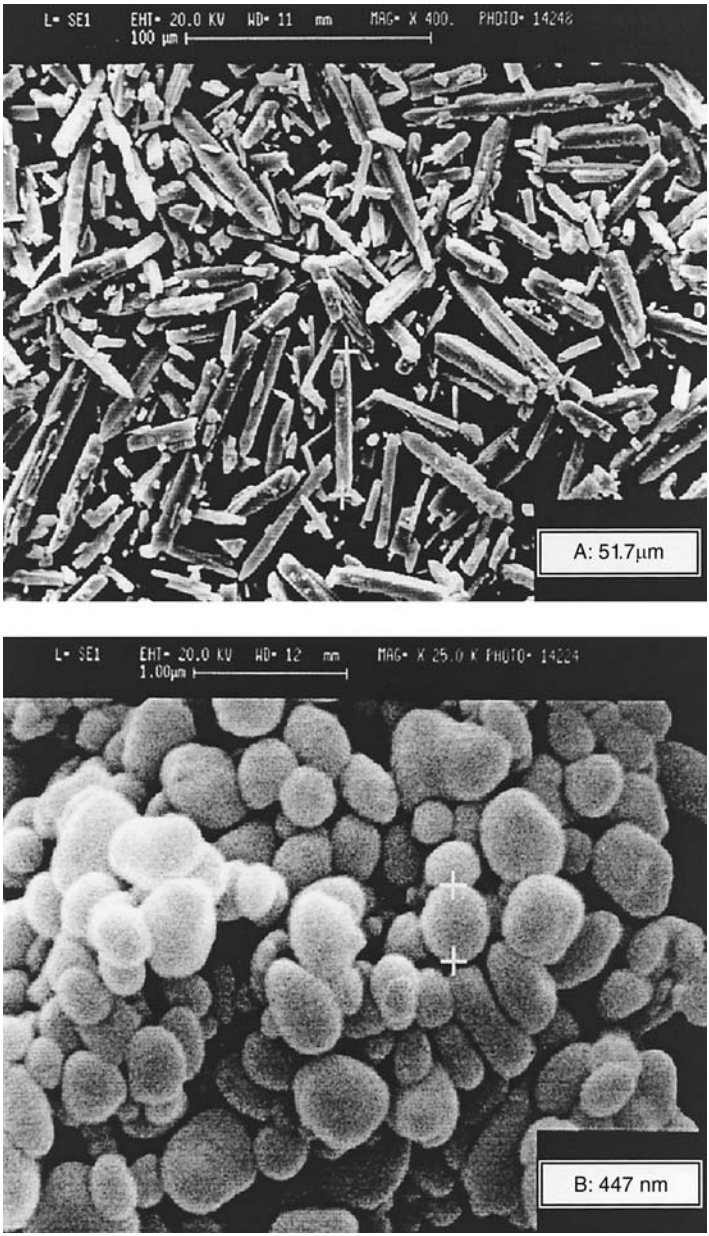


Figure 1 IDD micronization. The IDD micronization process produces homogeneous suspensions of surface-stabilized submicrometer-sized particles of water-insoluble drugs. Electron micrograph A shows 50–100 µm particles of a native model drug with a water solubility of approximately 40 µg/mL (distance between the markers ~51.7 µm). The IDD process yields surface-stablized submocrometer-sized drug particles, as shown in electron micrograph B (distance between markers ~447 nm). Surface stabilization may be elicited by phospholipids alone or mixtures of phospholipids and other surfactants.

Copyright © 2003 Marcel Dekker, Inc.

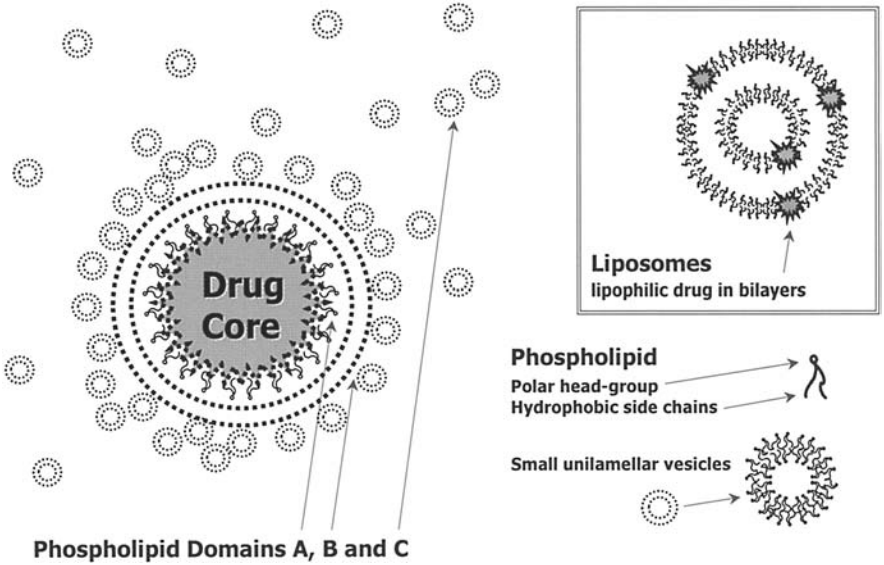


Figure 2 Schematic illustration of the IDD system and lipsome. The IDD system consists of a submicrometer-sized water-insoluble drug core stabilized with phospholipids with or without other surface modifiers. IDD-P formulations, a microparticulate variation of the IDD drug delivery system, consist of pure solid drug in the core of the particle. Similarly, in the IDD-D formulations (the microdroplet variation) the core is constituted of essentially liquid drug substance. Three distinct phospholipid domains are thought to exist in these formulations. The phospholipid molecules of *Domain A* are considered closely associated with the drug core. This domain may consist of the phospholipid molecular coating on the drug core. *Domain B* may be composed of more phospholipid layers and/or small unilamellar vesicles loosely associated with the core. Multiple phospholipid bilayers, typical of multilamellar liposomes, seem to be absent in the IDD-P or IDD-D formulations as evidenced by their X-ray diffraction and DSC profiles (unpublished results). Within the suspensions *Domain B* is thought to move with the drug core and gives the particle its hydrodynamic size. *Domain C* is composed of small bilayer vesicles and/or other phospholipid microstructures freely dispersed in the aqueous vehicle. A small fraction of the formulated drug may remain partitioned in the phospholipid microstructures of *Domains B* and *C*. In the case of IDD-D formulations, depending on the phospholipid solubility in the liquid drug, a small and undetermined amount of phospholipid may be dissolved in the lipophilic liquid drug core. On the other hand, liposomes are phospholipid bilayer vesicles. Lipophilic drugs are usually formulated with multilamellar vesicle liposomes composed of many concentric bilayers (only two bilayers are shown here). The lipophilic drug molecule is incorporated in the phospholipid bilayers that are separated by aqueous medium. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

Table 3 Attributes of Some Lyophilized IDD-P Formulations

Active ingredient		Phospholipids		Additional surfactants (amount)			Bulking agent				Volume weighted mean particle diameter; $D_{4,3}$ (μm)	
Name	Amount	Name	Amount	Myrj 52	PVP 17	NaDeox	Type	Qty	Type	Qty	Aqueous suspension before lyophilization	After lyophilization and resuspension with water
CTM	30.3	E80	9.1			—	SUC	45.5	SOR	15.1	0.97	0.98
ITR	27.8	E80	11.1			—	TRE	33.3	LAC	27.8	1.15	1.15
ITR	38.4	E80	15.4			—	TRE	46.2	—	—	1.15	1.12
CyA	21.1	P100H	8.4	4.2		1.0	MAN	23.2	LAC	42.1	0.92	1.33
CyA	29.9	P100H	11.9	6.0	17.9	1.5	MAN	32.8	—	—	0.91	1.08

Composition and drug loading (% w/w) of some lyophilized IDD-P formulations are shown together with volume-weighted mean particle diameter of the parent aqueous suspension and after resuspending the lyophilized powder with water to original composition. CyA = cyclosporine; E80 = lipoid E80; CTM = CTM650, a water-insoluble model drug; ITR = itraconazole; MAN = mannitol; NaDeox = sodium deoxycholate; P100H = phospholipon 100H; PVP17 = polyvinyl pyrrolidone; SOR = sorbitol; SUC = sucrose; TRE = trehalose; LAC = lactose.

Copyright © 2003 Marcel Dekker, Inc.

C. Payload

The presence of essentially pure drug material within the IDD-P particle core results in very high drug payloads, e.g., 200 mg/mL in IDD-P suspension [10,11] and up to 38% w/w in lyophilized IDD-P formulations (Table 3 [11]). Drug: phospholipid-vehicle ratio of as high as 10:1 w/w has been achieved in an IDD-P formulation of a triazole-antifungal drug (unpublished data). Much lower insoluble drug payloads are found in other non-IDD phospholipid formulations; e.g., liposomal or lipid-complex formulations of amphotericin B, AmBisome®, Abelcet®, and Amphotec® display drug:vehicle ratios of 0.14:1, 1:1, and 1:1 (w/w), respectively [10].

III. MANUFACTURING PROCESS

Fundamental unit operations that can be employed to generate small particles of IDD-P systems include (a) particle fracture processes and (b) particle nucleation processes. High shear, cavitation, or impaction (e.g., milling, attrition, homogenization, microfluidization, etc.) is employed for the drug particle fracture. Alternatively, ultrasmall drug nuclei are generated from a pressurized fluid solution of the drug substance in the second process. The presence of the phospholipid and/or other surface modifiers is essential for the formation and stability of the IDD-P systems by both processes. Association of phospholipid with or without other surface modifiers onto the freshly generated drug surface provides a capsule domain that prevents particle growth by aggregation, flocculation, agglomeration, or Ostwald ripening* during production and shelf life. Batch sizes as small as 20 g and containing as low as 50 mg of water-insoluble drug substance have been practiced at the feasibility stage.

A. Particle Size Reduction

While a number of alternative processes derived from the above principles could be employed, a typical manufacturing process consisting of commonly practiced pharmaceutical unit operations is outlined in the following scheme (Fig. 3). As a case study, this particular process, utilized to scale-up to 50-kg batches of an IDD-P formulation, is centered on a particle size reduction step by and M-210B Microfluidizer® (Microfluidics, Newton, MA). A 15-horsepower electric-hydraulic double-acting intensifier pump subjects an aqueous suspension product stream to pressures ranging from 2500 to 30,000 psi as it is directed through an

* Ostwald ripening refers to growth of larger crystals at the expense of dissolution of highly energetic smaller particles.

Copyright © 2003 Marcel Dekker, Inc.

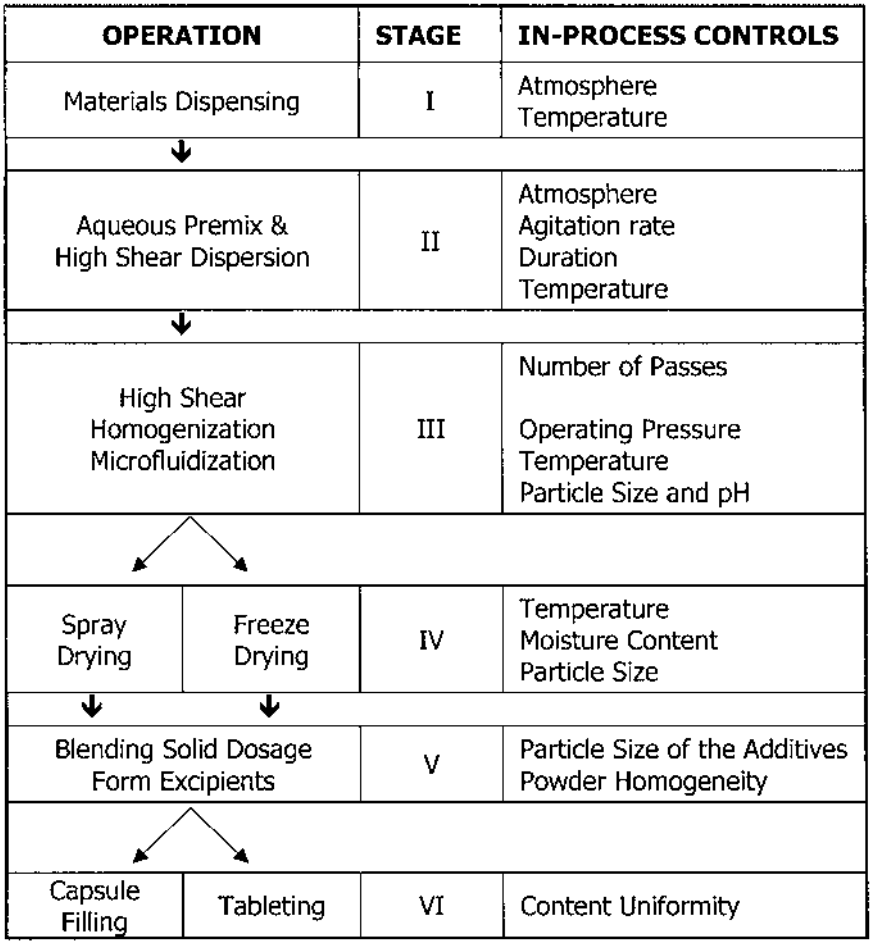


Figure 3 IDD-P unit operations. A schematic representation of a typical manufacturing process of IDD-P formulations shows a case study that was utilized to scale-up to 50-kg batches centered on the particle size reduction step by an M-210B Microfluidizer (Microfluidics, Newton, MA). Typical in-process controls of each unit operation are also shown.

interaction chamber (Fig. 4). Within the chamber are specially designed fixed-geometry microchannels through which the product accelerates to high velocities. This creates forces of high shear and impact as the product stream impinges upon itself and on wear-resistant diamond surfaces and then exits to ambient pressure. Because this process imparts high energy to the product stream, the latter is

Copyright © 2003 Marcel Dekker, Inc.

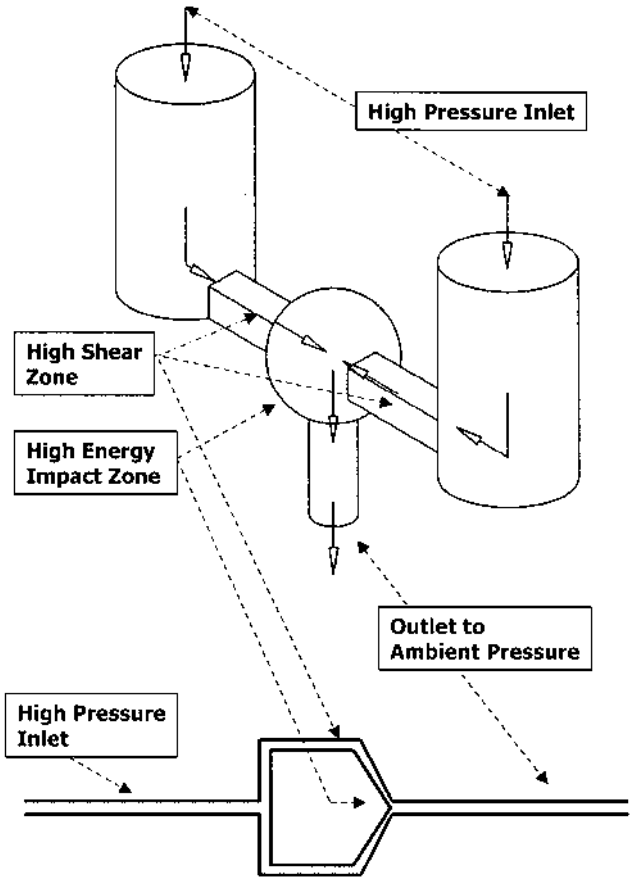


Figure 4 Interaction chamber of a Microfluidizer materials processor: Schematic illustrations of the product stream within the microchannels of a Microfluidics® interaction chamber. An electric hydraulic intensifier pump (not shown) drives the product stream into this chamber at a desired pressure and constant volume flow rate. Within the chamber are fixed-geometry microchannels of less than 100 μm internal dimensions through which the product accelerates to very high velocities creating high shear and impact forces as the product stream impinges upon itself and on diamond wear-resistant surfaces. On exit of the high-velocity microchannels the product fluid is suddenly released to ambient pressure within the high-energy impact zone. The particle size reduction occurs in the impact zone due to combined forces of high shear and impact. (Adapted from an illustration provided by Microfluidics, a Division of MFIC Corporation, Newton, MA)

Copyright © 2003 Marcel Dekker, Inc.

cooled with a heat exchanger after exiting from the interaction chamber. In this way the suspension is recirculated for the desired number of passes that bring about the suitable particle size reduction and facilitates the surface modifier association with the newly formed drug surfaces that result from particle fracture.

Acceptability of microfluidization as a unit operation in the pharmaceutical industry has been very well established. For instance, many large-scale pharmaceutical processes based on microfluidizers are reported for liposomes, emulsions, nanospheres, and cell-rupture-related unit operations [35–39]. Many processes in the chemical industry have been reported that use a microfluidizer for solid-particle size reduction [40]. While merits of this unit process for surface-modified particulate suspensions have been discussed [41], particle size reduction of water-insoluble drugs by microfluidization appears to be a pioneering adaptation of this process at pilot as well as commercial scale manufacture of IDD-P formulations.

B. Particle Growth from Solution

Several elegant, very simple, yet easily scalable supercritical fluid (SCF)-based processes have been developed for IDD-P formulations that employ controlled growth of solid drug nuclei from solution phase rather than size reduction unit operations. For example, stable microparticle suspensions of IDD-P cyclosporine (CyA), a water-insoluble drug, have been produced by rapid expansion of SCF solution to aqueous solution or suspension (RESAS) [42,43] of surface modifiers to minimize growth of the drug particles, which might otherwise occur in the free jet expansion. The particles were an order of magnitude smaller than those produced by free jet expansion into air without the surfactant solution. Hydrophilic excipients, such as bulking or matrix-forming agents, lyo or cryoprotectants, and pH buffers were also added into the aqueous surface modifier phase.

In an alternative approach, the product of a rapid expansion of liquefied gas solution (RELGS) of water-insoluble drugs can be optionally homogenized (RELGS-H process) at high pressure [44]. The homogenization step is thought to enhance the surface modifier interaction with the surface of the IDD-P particles and possibly further generate the necesary microstructures of the phospholipids typical of IDD formulations (see Fig. 2). RELGS or RELGS-H experiments run at different batch sizes (e.g., 200 mL and 2 L) have demonstrated the feasiblity and scalability of the SCF-based process for IDD-P products.

Particle sizes determined by photon correlation spectroscopy of some IDD-P CyA formulations made via RELGS and RELGS-H processes with purified egg lecithin, polysorbate or polyethoxylated caster oil, and mannitol are given in Table 4. These suspensions usually display Gaussian particle size distribution (e.g., Fig. 5) with a mean diameter within 100–500 nm. Occasionally

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Particle Size and Short-Term Stability of Some IDD-P Cyclosporine Formulations Prepared by RELGS and RELGS-H Process

	Volume-weighted mean particle diameter (nm)		
Formulation ID	After RESAS	After homogenization	At the stability time point
CS74	290	Not Homogenized	293 (5 days)
CS64H	349	237	273 (18 days)
			348 (34 days)
CS63H	303	342	323 (5 days)
			516 (39 days)
CS73H	146	214	227 (5 days)
CS76H	Bimodal	1 pass	349 (1 day)
	158 (33%)	Bimodal	
	~1500	151 (43%)	
	(67%)	1008 (57%)	773 (4 days)
		10 passes	
		217	364 (5 days)

a bimodal distribution may occur, as displayed by the formulation CS76H (Table 4) with a population at 158 nm (33%) and another at approximately 1500 nm (67%). There is little change in the particle size distribution of these formulations after one or two passes of high-pressure homogenization, for example with a traditional small orifice high-pressure homogenizing device such as an Avestin Emulsiflex C50 homogenizer (Avestin Inc., Ontario, Canada) (Table 4). The formulation CS76H is an exception again in that one-pass homogenization caused some size reduction, but did not change the bimodality of the particle size distribution. However, repeated homogenization of CS76H for 10 passes resulted in a size reduction to a mean diameter of 217 nm with a monomodal Gaussian distribution. Also, high-pressure homogenization after the RELGS process improves the particle size stability of this formulation for reasons detailed above [44].

C. Solid Dosage Forms

IDD-P suspensions obtained via RELGS/RELGS-H have demonstrated satisfactory particle size stability duration (Table 4), so that freeze drying, spray drying, or other drying methods can be initiated before any significant change in particle size can occur.

SEM visualization (Fig. 6) of a dried sample of a 39-day-old suspension of CS63H shows particles of approximately 200–400 nm diameter, which is in

Copyright © 2003 Marcel Dekker, Inc.

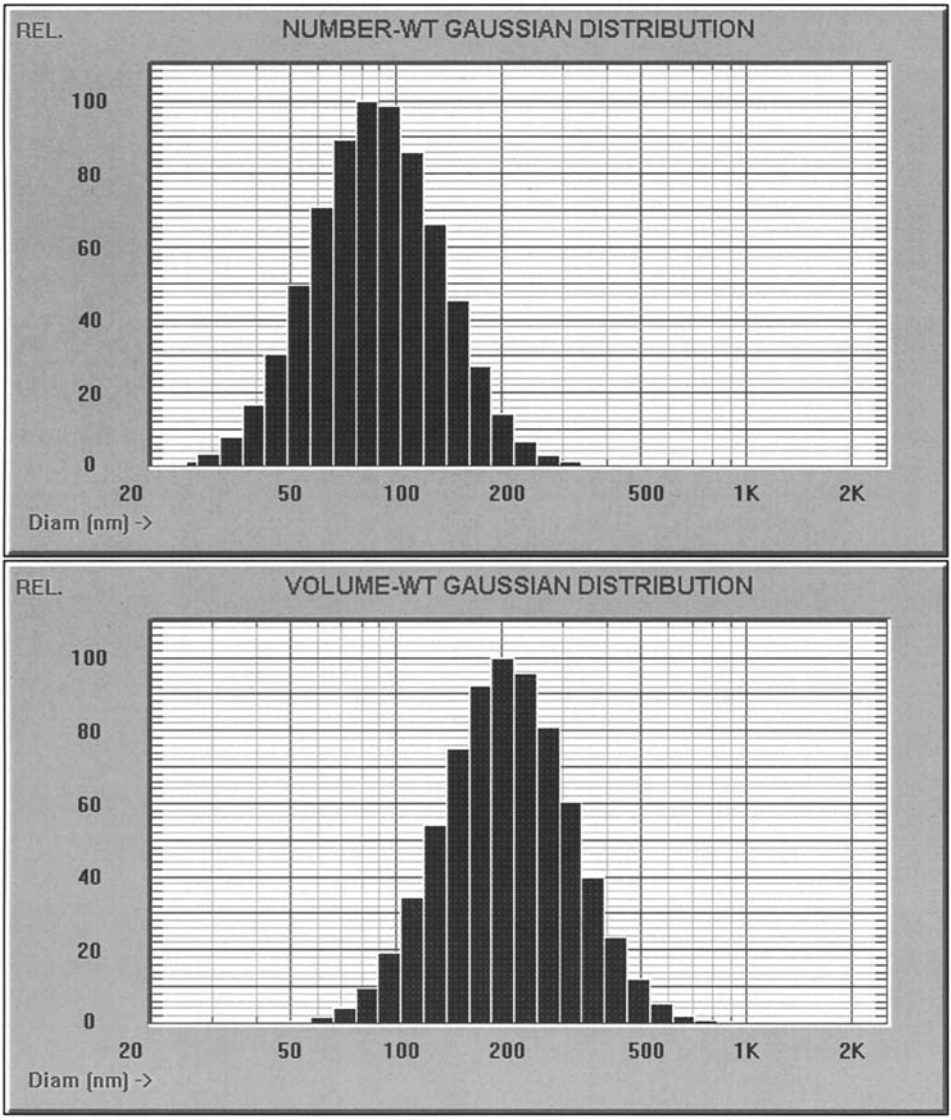


Figure 5 Particle size distribution of IDD-P product of RELGS-H process. Particle size distribution of an IDD-P CyA formulation produced by RELGS-H processes (rapid expansion of liquefied gas solution followed by homogenization) was determined by photon correlation spectroscopy using Nicomp 370 (Particle Sizing Systems, Santa Barbara, CA). Lower panel shows the volume-weighted Gaussian distribution with a mean of 226 nm and 99% of the particle population less than 516 nm. Upper panel is another representation of the same measurement displaying a much smaller mean diameter of 98 nm and 99% population of less than 224 nm when number-weighted distribution is plotted. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

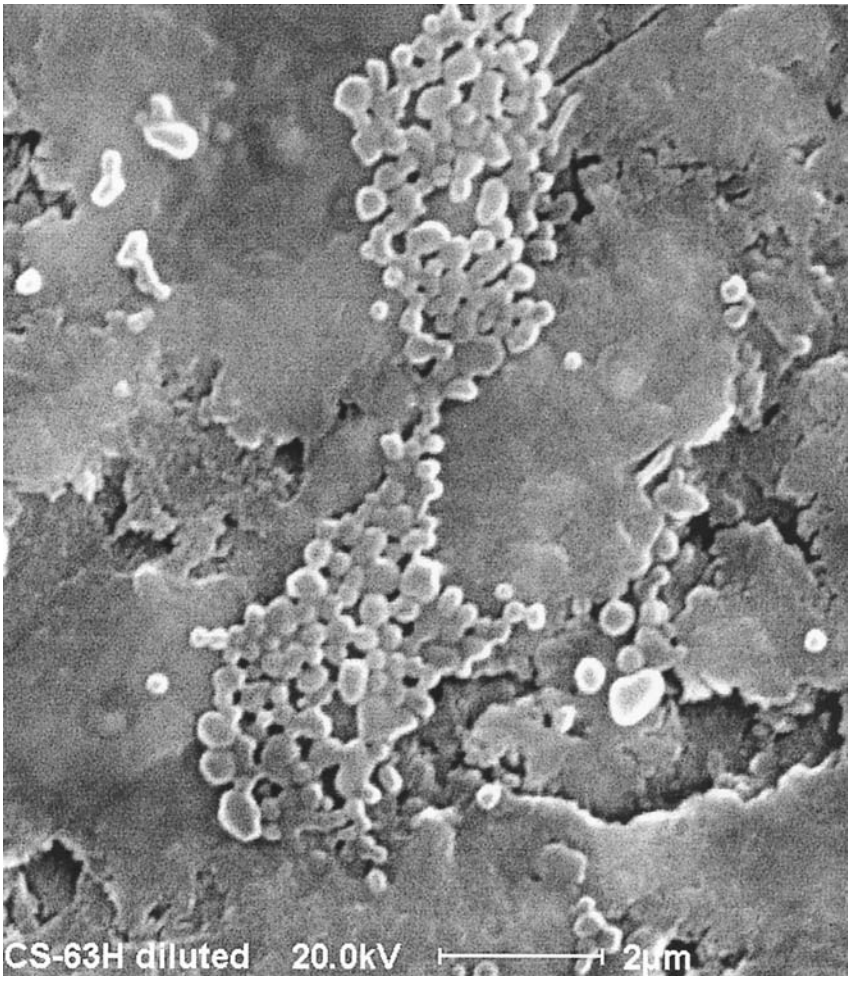


Figure 6 SEM visualization of IDD-P. Scanning electron micrography was performed with a JEOL 840A (accelerating voltage: 20 KeV, probe current: 1.0×10^{-9} amp) from an overnight dried sample on an aluminum stub and sputter coated approx. 10 nm with Au/Pd. This image shows IDD-P-CyA particles formed by the RELGS-H process with a size distribution similar to that obtained by photon correlation spectroscopy (see Fig. 5). The rough irregular features in the background of the particles are consistent with the morphology of the aluminum stub sample holder. Some particles appear agglomerated, as is expected with an IDD-P suspension sample dried at ambient temperature under vacuum on the aluminum stub for SEM visualization. Nevertheless, redispersiblity of lyophilized product to original particle size distribution has been demonstrated (see text).

Copyright © 2003 Marcel Dekker, Inc.

good agreement with photon correlation spectroscopic particle size data (Table 4). In this image, some particles appear agglomerated, as is expected with an IDD-P suspension sample dried at ambient temperature under vacuum on the aluminum stub for SEM visualization.

Suitability of the drying unit operations for IDD-P suspensions has been further established by reconstitution of dried formulations with aqueous media [10,45]. For instance, IDD-P suspensions of CTM650 (a water-insoluble model drug), cyclosporine, and itraconazole prepared by microfluidization were lyophilized and reconstituted with simulated gastric fluid to original particle size distribution (Table 3). Agents such as sucrose, α,α-trehalose, and mannitol were added to protect the microstructure of these formulations during lyophilization.

In certain cases where liquid suspensions of IDD-P formulations may display instability over extended periods of time, a lyophilized or otherwise dried product provides preferred dosage forms that allow the maintenance of particle size upon reconstitution. For example, lyophilized IDD-P bupivacaine [11] and busulfan [46] formulations have been developed that can be easily reconstituted with Water-for-Injection prior to administration.

IV. PHARMACEUTICAL CHARACTERISTICS

A. Stability

Depending on the drug, IDD formulations display excellent physical and chemical stability. An IDD-P CTM650 lyophilized formulation packaged in hard gelatin capsules displayed good physicochemical stability at various temperatures of storage between 2–8°C and 40°C (Table 5). As a further example, particle size of an IDD-P itraconazole formulation suffered negligible change under a variety of stress conditions, including freeze/thaw, thermal cycling between 2–8°C and 40°C, shaking, sedimentation by centrifugation, lyophilization followed by reconstitution, and even steam sterilization [10]. The Ostwald ripening effect has been minimized in IDD-P suspensions by the phospholipid surfaced modifiers. For instance, there was no evidence of any crystal growth in an IDD-P itraconazole suspension formulation on storage at ambient temperature for up to 6 months [10].

B. Release Profile and Bioavailability

The combination of the physical characteristics of each of the components of an IDD-P formulation offers a unique opportunity to control the pharmacokinetics and drug release mechanism of the formulated suspension. Thus, IDD-P formulations can display rapid release profiles when formulated with appropriate excipi-

Copyright © 2003 Marcel Dekker, Inc.

Table 5 Stability and Dissolution Profile of an Example IDD-P CTM650 Formulation

Test	Specifications	Initial	2 weeks	1 month	3 months	6 months
Assay	90.0–110.0% of label claim	98.9%	97.3%	97.3%	97.4%	96.1%
Dissolution	Mean ± standard deviation	101 ± 3%	95 ± 4%	93 ± 3%	92 ± 4%	76 ± 21%
	30 min	96 ± 3%	94 ± 3%	93 ± 2%	92 ± 4%	91 ± 6%
	60 min					
Water Content	Not more than 5%	1.9%	1.5%	1.5%	3.0%	1.9%
Particle size (μm)	Report volume weighted mean diameter ($D_{4,3}$)	5.0	2.9	3.3	4.9	5.2

Hard gelatin capsules containing lyophilized IDD-P CTM650 formulation were packaged in HDPE plastic bottles with polypropylene cap along with a desiccant packet and stored at 2–8°C/ambient relative humidity (RH), 25°C/60% RH, and 40°C/75% RH. Stability data for 25°C/60% RH storage are shown here. Drug assay was determined with a reverse-phase high-performance liquid chromatography method. The dissolution test method used a USP Dissolution Apparatus II—paddles revolving at 75 RPM in a medium of 0.1 M sodium dodecyl sulfate at 37°C. Each capsule was weighted and placed in a coil wire sinker. Five-milliliter samples were aliquoted at desired time points, filtered through a 0.45-μm filter, and diluted 1:5 with fresh dissolution medium. Samples were analyzed using a UV spectrophotometer at a wavelength of 296 nm. Water content was determined by Karl-Fischer titration. Particle size distribution was measured by a laser diffraction apparatus, Malvern Mastersizer Microplus (Malvern, Worcestershire, UK).

Copyright © 2003 Marcel Dekker, Inc.

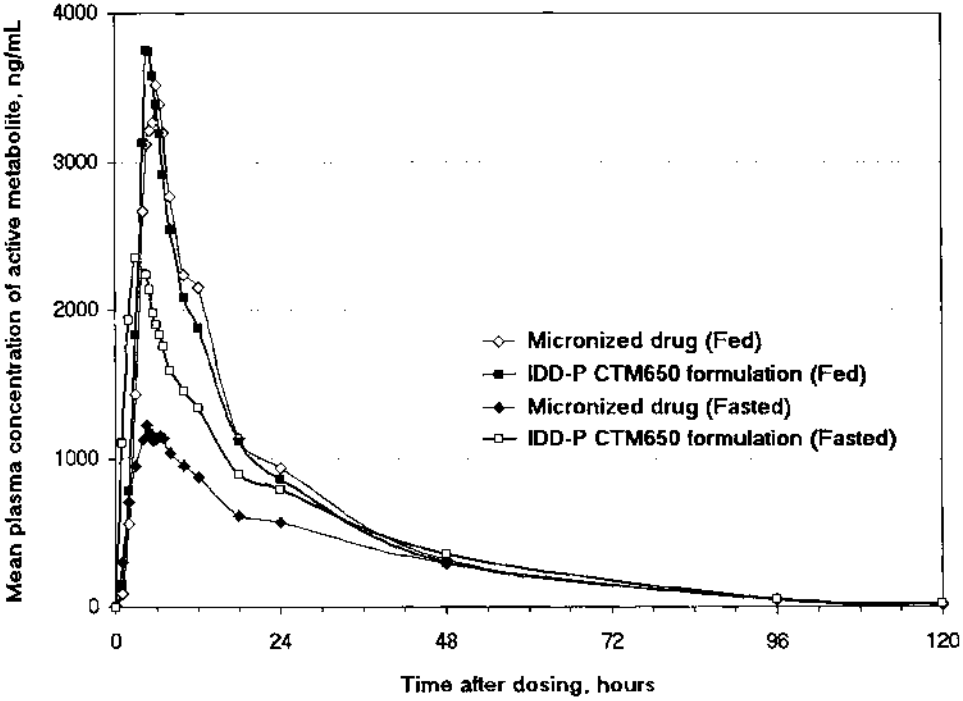


Figure 7 Oral pharmacokinetics of IDD-P CTM650 formulation and micronized drug in healthy human volunteers. Plasma concentration of active metabolite versus time curves demonstrate oral bioavailability improvement by IDD-P formulation. A single dose of IDD-P formulation of CTM650 in hard gelatin capsule and micronized drug in hard gelatin capsules were orally administered to healthy human volunteers ($n = 8$) under fed and fasted conditions for an oral pharmacokinetic comparison. This was a randomized, open-label, four-treatment-period crossover, single-center study.

ents and provide examples of improvement in bioavailability of water-insoluble drugs. IDD-P CTM650 formulation (Table 5) shows almost complete dissolution of the drug within 1 h. While surface area increase by size reduction of the particulate formulations is a commonly believed factor behind bioavailability improvements, one cannot rule out formulation intervened absorption enhancement as indicated by a pharmacokinetics study with an IDD-P CTM650 formulation in human subjects.

CTM650 is a water-insoluble and poorly absorbed drug. The original formulation was improved by micronization to give a product that demonstrated better absorption and allowed a reduction of the daily dose. A pharmacokinetic

Copyright © 2003 Marcel Dekker, Inc.

comparison of a single dose of CTM650 in the form of a dried free-flowing powder of IDD-P formulation placed in two-piece natural hard gelatin capsule and micronized drug in hard gelatin capsule was performed in healthy human volunteers under fed and fasted conditions. The study was designed as a four-treatment, four-period, open-label, randomized-sequences crossover study with eight healthy male volunteers aged 18–40 years. Ten days washout interval was allowed between the treatment periods. The four treatments were: (a) one IDD-P CTM650 formulation in hard gelatin capsule dosed in fasted condition; (b) one micronized drug capsule dosed in fasted condition; (c) one IDD-P CTM650 formulation in hard gelatin capsule dosed in fed condition; and (d) one micronized drug capsule dosed in fed condition. The first two periods were fasted and the last two fed conditions. For fasted conditions A and B, the capsules were administered following a 10-h overnight fast. For treatments C and D, the formulations were administered within 5 min following a standardized meal (given after a 10-h overnight fast) that provided approximately 850 Kcal with more than 50% of calories from fat origin. In all the treatments a postdose meal was served 4 h after the drug administration. Blood samples were withdrawn before dosing the test or reference formulations and at various time points until 120 h after dosing for measurement of plasma concentrations of the active metabolite.

The pharmacokinetic profile of this study is shown in Figure 7 as the mean concentration of active metabolite of the drug in plasma obtained from the four treatments. No significant adverse events were observed. The mean plasma concentration curves indicate that IDD-P CTM650 formulation is bioequivalent to micronized drug when taken with a fat-rich meal.* $AUC_{0\text{-inf}}$ and C_{max} for IDD-P CTM650 formulation and micronized drug are almost identical. The ratios are, respectively, 97% and 96%. However, IDD-P CTM650 formulation is not bioequivalent to micronized drug when taken in the fasting state, its bioavailability being about twice that of micronized drug. In the fasting state, IDD-P CTM650 formulation appears to be better absorbed than the micronized drug in all subjects, and the mean $AUC_{0\text{-inf}}$ is 49% higher.

The IDD-P formulation modifies the digestive absorption and bioavailability characteristics over micronized formulations. In the fasting state, the bioavailability is almost 50% higher with IDD-P CTM650 formulation compared to micronized drug. Therefore, it is predicted that the same plasma concentration will be achieved with a dosage form of IDD-P formulation of CTM650 of reduced potency.

* As per FDA's 1997 Draft Guidance: 2 eggs fried in butter, 2 slices of bread toasted with butter, 25 g butter, 2 strips of bacon, 110 g hashed brown potatoes, 280 g of whole milk.

Copyright © 2003 Marcel Dekker, Inc.

V. SAFETY AND REGULATORY ISSUES

The use of harsh excipients, such as large quantities of certain surfactants, is a major concern in evaluating safety of modern delivery techniques for water-insoluble drugs. For instance, there is a recommended upper limit of daily intake of some widely used surfactants: 25 mg/kg/day for sorbitan fatty acid esters [47,48], polysorbates [47], and povidone [49] and 10 mg/kg/day for polyethyleneglycols [50]. The IDD formulation approach substantially eliminates the risk of side effects by the use of phospholipids that are cell membrane components and consumed as a normal part of the diet. They have a long history of use and safety in pharmaceutical formulations. Large oral dosages of phospholipids of up to 80g/day have been reported [51]. As a result of their endogenous nature in mammalian systems, phospholipids are acceptable to regulatory agencies for oral as well as parenteral administration. Formulations containing phospholipids have toxicities comparable to or less than those of unformulated drug and are highly tissue compatible.

VI. COMPETITIVE ADVANTAGE AND FUTURE DIRECTIONS

The reliance on a major physical property of the drug, i.e., its water insolubility, rather than on a specific chemical property, facilitates application of IDD technology to a broad range of insoluble drugs. Advantage can be taken of the spectrum of preparation scales available in IDD technology for the formulation and evaluation of a wide variety of both new and old compounds. Classes of water-insoluble compounds include newly discovered and promising water-insoluble drugs, proprietary drugs with excellent potential that remain shelved in pharmaceutical libraries because of perceived or prior inhouse difficulties with their formulation, and currently marketed drugs that may be otherwise less than adequately formulated for successful delivery or for which revised and improved formulation by IDD technology may offer improved patent life. Once a viable drug formulation is achieved on a small scale, it can be scaled up with little difficulty. Small-scale preparation capabilities in IDD technology make it a useful tool for relatively rapid in vivo evaluation of water-insoluble new chemical entities that result from in vitro research and often remain unexplored owing to lack of viable formulation. IDD technology encompasses insoluble drugs that are not limited by therapeutic and chemical classes, does not exclude lipid-soluble or lipid-insoluble drugs, and provides safe and efficacious products for a variety of administration routes. In addition to the inherent safety profiles associated with phospholipid particle stabilizers, IDD technology formulations have displayed high drug payload, low amount of free drug in the continuous phase, almost all of the drug present in

Copyright © 2003 Marcel Dekker, Inc.

the dispersed particulate phase, no chemical change in the drug caused by the formulation process, absence of drug-vehicle interaction, narrow particle size distribution with well-defined particle morphology, a variety of suspensions and solid dosage forms, excellent bioavailability when required, and long formulations shelf-lives.

Phase I and Phase II clinical trials have been completed with various IDD formulations for oral as well as injectable [10,11] administration. These have demonstrated excellent safety and efficacy profiles. Beyond bioavailability improvement of water-insoluble drugs by virtue of the small size of their particles and depending on the drug, IDD-P formulations used for oral administration can be formulated to modulate gastrointestinal absorption in part by the intervention of the biocompatible formulation components. Further development of IDD formulation systems employing new chemical entities and with new and improved formulations of currently available drugs show promise to provide decreased dosage levels of drugs for improved bioavailability, for bioequivalence at lower dose levels, and for increased efficiency in drug delivery.

Excellent reproducibility in scaleup for manufacturing IDD-formulated products has been achieved. Unlike liposomes, these formulations have not encountered any major scaleup problems. Formulating with traditional and GRAS-listed phospholipid excipients and the absence of any vehicle for formulation related side effects is expected to facilitate regulatory approval of IDD formulations.

REFERENCES

1. D Fleisher, C Li, Y Zhou, LH Pao, A Karim. Drug, meal and formulation interactions influencing drug absorption after oral administration: clinical implications. Clin Pharmacokinet 36:233–254, 1999.
2. LL Ponto, RD Schoenwald. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (Part I). Clin Pharmacokinet 18:381–408, 1990.
3. J Posti, K Katila, T Kostiainen. Dissolution rate limited bioavailability of flutamide, and in vitro–in vivo correlation. Eur J Pharm Biopharm 49:35–39, 2000.
4. HM Abdou. Methods for enhancement of drug dissolution characteristics. Dissolution, Bioavailability & Bioequivalence. Easton, PA: Mack Publishing Company, 1989, pp. 265–284.
5. HC Ansel, NG Popovich. Dosage from design. In: HC Ansel, NG Popovich, eds. Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lea & Febiger, 1990, pp. 56–58.
6. DH Haynes. Microdroplets of water insoluble drugs. International patent W085/00011, 1985.

Copyright © 2003 Marcel Dekker, Inc.

7. DH Haynes. Method of inducing local anesthesia using microdroplets of a general anesthetic. US patent 4,622,219, 1986.
8. DH Haynes. Phospholipid-coated microcrystals: injectable formulations of water-insoluble drugs. US patents 5,091,187 and 5,091,188, 1992.
9. DH Haynes. Microdroplets of water-insoluble drugs and injectable formulations containing same. US patent 4,725,442, 1988.
10. SN Pace, GW Pace, I Parikh, AK Mishra. Novel injectable formulations of insoluble drugs. Pharm Technol 23:116–134, 1999.
11. A Mishra, G Robinson, G Pace. Novel injectable formulations of water-insoluble drugs. Controlled Release Newslett 17:21–30, 2000.
12. GG Liversidge, KC Cundy, JF Bishop, DA Czekai. Surface modified drug nanoparticles. US patent 5,145,684, 1992.
13. KJ Illig, P Sarpotdar. Formulations comprising Olin 10-G to prevent particle aggregation and increase stability. US patent 5,340,564, 1994.
14. HW Bosch, DM Marcera, RL Mueller, JR Swanson, DS Mishra. Process for preparing therapeutic compositions containing nanoparticles. US patent 5510118, 1996.
15. RH Muller, R Becker, B Kruss, K Peters. Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution. US patent 5,858,410, 1999.
16. PP Speiser. Nanoparticles and liposomes: a state of the art. Methods Find Exp Clin Pharmacol 13:337–342, 1991.
17. J Kreuter. Nanoparticles. In: J Kreuter, ed. Colloidal Drug Delivery Systems. New York: Marcel Dekker, 1994, pp. 219–342.
18. H Okada, H Toguchi. Biodegradable microspheres in drug delivery. Crit Rev Ther Drug Carr Syst 12:1–99, 1995.
19. JC Wunderlich, U Schick, J Werry, J Freidenreich. Gelatin or collagen hydrolysate containing drug formulation that provides for immediate release of nanoparticle drug compounds. US patent 5,932,245, 1999.
20. D Bar-Shalom, T Kindt-Larsen. Controlled release erodible composition. US patent 5,618,560, 1997. See also http://www.egalet.dk/home.htm.
21. JG Devane, S Mulligan, M Kavanagh, SD Davis, RA Sparrow, IR Wilding. New developments in sustained-release antihypertensive therapy: formulation and pharmacokinetic considerations. Am J Cardiol 69:23E–27E, 1992. See also http://www.elan.ie/drugdel/technologies/oral/indas.asp.
22. RH Muller, K Mader, S Gohla. Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. Eur J Pharm Biopharm 50:161–177, 2000.
23. MNS Santos, S Benita, M Seiller. Les emulsions orales: obtention et biodisponibilite (Oral emulsions: preparation and bioavailability). J Pharm Belg 48:211–226, 1993.
24. JA Rogers, KE Anderson. The potential of liposomes in oral drug delivery. Crit Rev Ther Drug Carr Syst 15:421–480, 1998.
25. T Gershanik, S Benita. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. Eur J Pharm Biopharm 50:179–188, 2000.
26. S Tenjarla. Microemulsions: an overview and pharmaceutical applications. Crit Rev Ther Drug Carr Syst 16:461–521, 1999.
27. AT Serajuddin. Solid Dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthoughs. J Pharm Sci 88:1058–1066, 1999.

Copyright © 2003 Marcel Dekker, Inc.

28. BA Klyashchitsky, AJ Owen. Drug delivery systems for cyclosporine: achievements and complications. J Drug Target 5:443–458, 1998.
29. PP Constantinides. Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm Res 12:1561–1572, 1995.
30. DO Thompson. Cyclodextrins-enabling excipients: their present and future use in pharmaceuticals. Crit Rev Ther Drug Carr Syst 14:1–104, 1997.
31. BJ Aungst. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. J Pharm Sci 82:979–987, 1993.
32. I Genta, P Perugini, F Pavanetto, T Modena, B Conti, RA Muzzarelli. Microparticulate drug delivery systems. EXS 87:305–313, 1999.
33. J Lansman, DH Haynes. Kinetics of a CA^{2+}-triggered membrane aggregation reaction of phospholipid membranes. Biochim Biophys Acta 394:335–347, 1975; and unpublished data.
34. DH Haynes, AF Kirkpatrick. Ultra-long duration local anesthesia produced by intradermal injection of lecithin-coated methoxyflurane microdroplets. Proc Int Symp Control Rel Bioact Mater 14:293–294, 1987.
35. A Vivier, JC Vuillemard, HW Ackermann, D Poncelet. Large-scale blood substitute production using a microfluidizer. Biomater Artif Cells Immobiliz Biotechnol 20: 377–397, 1992.
36. MD White, D Marcus. Disintegration of microorganisms. Adv Biotechnol Processes 8:51–96, 1988.
37. DM Lidgate, T Trattner, RM Shultz, R Maskiewicz. Sterile filtration of a parenteral emulsion. Pharm Res 9:860–863, 1992.
38. R Bodmeier, H Chen, P Tyle, P Jarosz. Spontaneous formation of drug-containing acrylic nanoparticles. J Microencapsul 8:161–170, 1991.
39. DM Lidgate, RC Fu, NE Byars, LC Foster, JS Fleitman. Formulation of vaccine adjuvant muramyldipeptides. 3. Processing optimization, characterization, and bioactivity of an emulsion vehicle. Pharm Res 6:748–752, 1989.
40. http://www.microfluidicscorp.com/mi_ref.htm.
41. KJ Illig, RL Mueller, KD Ostrander, JR Swanson. Use of microfluidizer processing for preparation of pharmaceutical suspensions. Pharm Technol 20:78–88, 1996.
42. IB Henriksen, AK Mishra, GW Pace, KP Johnston, S Mawson. Insoluble drug delivery. WIPO WO9714407A1, 1997.
43. TJ Young, S Mawson, KP Johnstron, IB Henriksen, GW Pace, AK Mishra. Rapid expansion from supercritical to aqueous solution to produce submicron suspension of water-insoluble drugs. Biotechnol Progr 16:402–407, 2000.
44. GW Pace, MG Vachon, AK Mishra, IB Henriksen, V Krukonis, A Godinas. Processes to generate submicron particles of water-insoluble compounds. WIPO WO9965469A2, 1999.
45. I Parikh, AK Mishra, R Donga. MG Vachon. Dispersible phospholipid stabilized microparticles. WIPO WO030616A1, 2000.
46. W McCulloch, I Parikh, OM Colvin, G Parö. Development of I.V. busulfan (Spartaject-Busulfan). Annual Meeting of the European Group for the Bone Marrow Transplantation, Harrogate, UK, March 1994. pp. 116.

Copyright © 2003 Marcel Dekker, Inc.

47. FAO/WHO. Toxicological evaluations of certain food additives with a review of general principles and of specifications. Tech Rep Ser WHO 1974, No. 539.
48. FAO/WHO. Evaluations of certain food additives and contaminants. Tech Rep Ser WHO 1982, No. 683.
49. FAO/WHO. Evaluations of certain food additives and contaminants. Tech Rep Ser WHO 1983, No. 696.
50. FAO/WHO. Evaluations of certain food additives. Tech Rep Ser WHO, 1980, No. 648.
51. JH Growdon et al. Lecithin can suppress tardive dyskinesia. N Engl J Med 298: 1029–1030, 1978.

Copyright © 2003 Marcel Dekker, Inc.

14

Liquid-Filled and -Sealed Hard Gelatin Capsule Technologies

Ewart T. Cole
CAPSUGEL, a Division of Pfizer Inc., Arlesheim, Switzerland

I. INTRODUCTION

The hard gelatin capsule has been used for many years as an oral delivery form. Initially drugs in powdered or granular form were usually filled into the capsule to provide a unit dose that effectively masked the bitter taste of drugs in an easy-to-swallow container. With the advent of pellet technology to modify the release properties of drugs, the capsule provided an ideal vehicle into which multiparticulates could be filled without risk of modifying the release characteristics by compression into tablets [1]. More recently, technology has been developed to accurately dose and seal liquids into hard gelatin capsules [2–4] and this chapter will review the areas of application of this technology, outline the requirements of the formulation, compare it with soft gelatin capsule technology, and describe a process for sealing hard gelatin capsules.

II. DRUG CHARACTERISTICS RELEVANT TO LIQUID FILLING TECHNOLOGY

Table 1 summarizes the various characteristics of drugs for which liquid filling technology is applicable. For almost all categories of drugs examples of marketed products are given to illustrate that several companies are already using the technology. Many more products are in various phases of the development process.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Drug Characteristics for Which Liquid-Filling Technology Is Relevant

Characteristic	References	Examples of marketed products
Poorly soluble	[5–11]	Nifedipine (Apricol®) Ibuprofen (Solufen®)
Short half-life requiring frequent dosing	[12–18]	Captopril (Captoril®)
Low melting point	[19]	Oils of avocado and soya (Piascledine®) Danthron (Co-danthramer)
Low dose/high potency	[12,19–21]	Products in development
Critical stability	[22–24]	Vancomycin hydrochloride (Vancocin®)

III. THE EMPTY HARD GELATIN CAPSULE IN COMPARISON TO SOFT GELATIN CAPSULES

The hard gelatin capsule for liquid filling is identical in composition to the capsule used for filling powders and comprises gelatin, water, and coloring and opacifying agents. For an efficient sealing process, however, it is important that the fill material does not penetrate into the zone between the body and cap before the sealing operation. A capsule with a special configuration has been designed to eliminate this (Licaps™) and a range of capsule sizes from approximately 0.3 to 0.85 mL is available. In contrast to the hard gelatin capsule, the soft gelatin capsule contains a plasticizer in addition to gelatin and water, and commonly glycerol at a level of approximately 30% is used. The soft gelatin capsule process has been reviewed by Jimerson [25] and a comparison of the two capsule types is given in Table 2.

IV. SUITABILITY OF FILL MATERIALS

As the tendency for poorly water-soluble drugs to enter the pipeline increases, so does the challenge to find innovative ways of developing bioavailable and stable dosage forms. Excipient suppliers, encouraged by the potential opportunities in this field, are developing new materials comprising mixtures of functional excipients. An example is the introduction of SMEDDS (Self-Emulsifying Drug Delivery System) by Gattefossé. Undoubtedly this approach was stimulated by the work performed by Sandoz, on the microemulsion formulation of cyclosporin A [10,11]. Bowtle [29] has described a process for selection of bases for thermosetting formulations.

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Characteristics of Hard and Soft Gelatin Capsules

Aspect	Hard gelatin capsule	Soft gelatin capsule	Reference
Inhouse development and manufacture	Yes	Difficult	
Ability to manufacture small batches	Yes	No	
Scale-up	Simple and inhouse	Requires large quantities of drug substance and must be outsourced	
Temperature of fill	Max. ~70°C	Max. ~35°C	[25]
Plasticizer in shell	No	Yes	[25,26]
Risk of drug migration	Low	High for drugs soluble in plasticizer	[27]
Permeability of shell to oxygen	Low	High due to plasticizer[a]	[21,28]
Sensitivity to heat and humidity	Low	High due to plasticizer	[26]
Limitation on excipients for formulation	High concentrations of hygroscopic excipients such as glycerol must be avoided	Hygroscopic excipients can be tolerated due to presence of plasticizer in shell	[25,26]
Capsule dimensions	Constant	May vary	

[a] Dependent on moisture content of shell.

As the potential for interactions between the capsule shell and fill are greater than is the case with a powder-filled capsule, techniques have been developed to monitor this.

A. Moisture Exchange Fill Shell

Typically a hard gelatin capsule contains 13.5–15.5% moisture, which acts as a plasticizer for gelatin. A hygroscopic material, when filled into the capsule, could extract moisture from the shell thereby inducing embrittlement. The potential for

Copyright © 2003 Marcel Dekker, Inc.

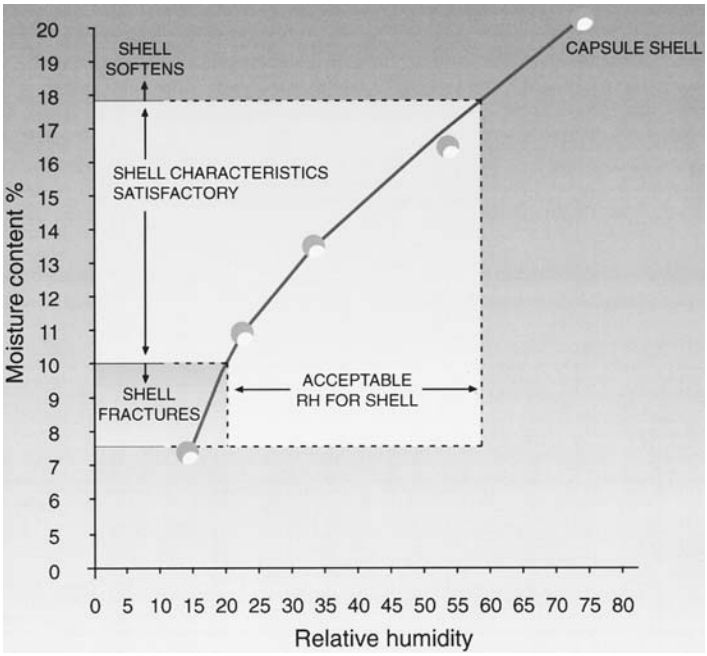


Figure 1 Equilibrium moisture content of empty gelatin capsules shells stored at various relative humidities for 2 weeks at 20°C. (From Ref. 31.) (See color insert.)

this is checked by storing capsules filled with the product under various conditions of relative humidity from 2.5 to 65% and measuring the weight change as already described by Cadé and Madit [30].

B. Mechanical Properties

The relationship between relative humidity during storage, gelatin moisture content, and capsule properties was reported by Bond et al. [31] and is shown in Figure 1. The change in capsule brittleness with relative humidity has also been studied by Kontny and Mulski [32]. It follows that monitoring of the mechanical properties of capsules stored at various relative humidities is of critical importance in determining compatibility between the fill material and the capsule shell. The methodology to determine this is described by Cadé and Madit [30].

C. Dissolution Stability Indicator

The potential for interaction of an excipient or active with the capsule shell that can result in a change in dissolution behavior has been described by Dey et al.

Copyright © 2003 Marcel Dekker, Inc.

[33] for capsules filled with powders. Dissolution of gelatin capsules was also the topic of an FDA/Industry Working Group, and a modified dissolution testing procedure allowing the use of enzymes has been accepted when a delay in dissolution is a result of pellicle formation [34]. No relevance to the in vivo behavior of the capsules was established [35,36].

Certain excipients used in the formulation of liquid-filled capsules may have, or may generate during storage, low levels of aldehydes, which can potentially react with gelatin. The technique to monitor any interaction is described by Cadé and Madit [30].

Particularly in the case of hot-melt fills the effect of melting temperature and time held at this temperature on the potential for formation of aldehydes needs to be investigated. The rate of cooling can also have an influence on the structure of certain excipients, which in turn may modify the drug release characteristics from the matrix itself [37].

D. Recommended Properties (Temperature and Viscosity) of Fill Materials

The important factors to bear in mind during a liquid filling operation are temperature and viscosity of fill material and, in the case of a suspension, the particle size of the suspended drug. Whereas in principle any excipient found to be compatible with the gelatin shell can be used, in practice in a manufacturing environment the viscosity of the fill material is important. If the viscosity is too low, splashing of the bushings may occur, which could contaminate the area of overlap between the capsule body and cap and prevent a good seal from being formed. Absence of a clean break during dosing (stringing) can have the same effect. The guidelines for problem-free filling are given in Table 3.

E. Excipients Compatible with Hard Gelatin Capsules

The materials listed have been tested according to the procedures described above. Excipients that, from the aspect of compatibility, can be considered to be

Table 3 Recommended Guidelines for Dosing Liquids/Semisolids into Hard Gelatin Capsules

Parameter	Recommendation
Temperature of fill material	Max. ~70°C
Viscosity at the temperature of dosing	0.1–1 Pa s
Dosing characteristics	Clean break from dosing nozzle Absence of "stringing"
Particle size of suspended drug	≤50 μm

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Lipophilic Liquid Vehicles Compatible with Hard Gelatin Capsules

Refined specialty oils	MCTs[a] and related esters
Arachis oil	Akomed E
Castor oil	Akomed R
Cottonseed oil	Captex 355
Maize (corn) oil	Labrafac CC
Olive oil	Labrafac PG
Sesame oil	Lauroglycol FCC
Soybean oil	Miglyol 810
Sunflower oil	Miglyol 812
	Miglyol 829
	Miglyol 840
	Softisan 645

[a] Medium-chain triglycerides.
Note: The quality may vary between different suppliers and also from batch to batch and should be routinely checked. The thermal history of excipients during manufacture should be recorded.

suitable for formulation of drugs into hard gelatin capsules are shown in Tables 4, 5, and 6. They have been classified into three arbitrary groups: lipophilic liquid vehicles, semisolid lipophilic vehicles/viscosity modifiers for lipophilic liquid vehicles, and solubilizing agents, surfactants, emulsifying agents, and adsorption enhancers.

Excipients shown in Table 7 are considered to be incompatible with hard gelatin capsules and should be avoided at high concentrations. They may, however, be used in mixed systems, in which case the critical concentration above which compatibility could become an issue must be determined experimentally. The compatibility screening of the final formulation including the drug substance must be monitored as part of the routine development process.

V. FILLING AND SEALING EQUIPMENT

A. Capsule-Filling Machines

Most of the modern European capsule-filling machines can be modified to allow hard gelatin capsules to be filled with hot or cold liquids. The machine requirements to allow an industrial manufacture of liquid-filled capsules are reported by Cole [38] and the models available are given in Table 8.

Copyright © 2003 Marcel Dekker, Inc.

Table 5 Semisolid Lipophilic Vehicles and Viscosity-Modifying Substances Compatible with Hard Gelatin Capsules

Hydrogenated speciality oils	
Arachis oil	Groundnut 36
Castor oil	Cutina HR
Cottonseed oil	Sterotex
Palm oil	Softisan 154
Soybean oil	Akosol 407
Aerosil	
Cetosteryl alcohol	
Cetyl alcohol	
Gelucires 33/01, 39/01, 43/01	
Glyceryl behenate (Compritol 888 ATO)	
Glyceryl palmitostearate (Precirol ATO 5)	
Softisans 100, 142, 378, 649	
Stearic acid	
Steryl alcohol	

Note: The quality may vary between different suppliers and also from batch to batch and should be routinely checked. The thermal history of excipients during manufacture should be recorded.

B. Equipment for Sealing Hard Gelatin Capsules

An essential part of a liquid-filling operation is the ability to effectively seal the capsule. Various methods are available to seal hard gelatin capsules and these have been reviewed by Wittwer [39]. The two most studied methods are banding using a gelatin band and sealing using a hydroalcoholic solution, and both methods are described in the General Information section of the USP on capsules [40]. Banding of hard gelatin capsules has been described by Bowtle [29].

The capsule sealing process, which was first described by Wittwer [39] and subsequently by Cadé et al. [21], uses the principle of lowering of the melting point of gelatin by the application of moisture to the area between the capsule body and cap. Figure 2 illustrates the process to bring the sealing fluid to the area of capsule overlap. The various stages of the process are outlined in Table 9.

The machine for industrially sealing hard gelatin capsules, shown in Figure 3, is commercially available and is marketed under the name LEMS™ 30* (Liquid Encapsulation by MicroSpray). The machine is free standing and in practice is connected to the output of a capsule-filling machine by means of a conveyor.

To allow manufacture of small batches for technical or clinical testing Cap-

* LEMS™ is a registered trademark of the Capsugel Division of Pfizer Inc.

Copyright © 2003 Marcel Dekker, Inc.

Table 6 Solubilizing Agents, Surfactants, Emulsifying Agents, and Adsorption Enhancers Compatible with Hard Gelatin Capsules

Capryol 90
Gelucire 44/14, 50/13
Cremophor RH 40
Imwitor 191, 308,[a] 380, 742, 780 K, 928, 988
Labrafil M 1944 CS, M 2125 CS
Labrasol
Lauric acid
Lauroglycol 90
Oleic acid
PEG MW $>$ 4000
Plurol Oleique CC 497
Poloxamer 124 and 188
Softigen 701, 767
Tagat TO
Tween 80

[a] Glycerin content $<$ 5%.
Note: The quality may vary between different suppliers and also from batch to batch and should be routinely checked. The thermal history of excipients during manufacture should be recorded.

Table 7 Excipients that Are Incompatible with Hard Gelatin Capsules when Tested Alone

Ethanol
Cremophor EL
Glycerin
Glycofurol 75
MCMs
Akoline MCM, Capmul MCM, Imwitor 308[a]
PEGs of MW $<$ 4000
Pharmasolve
Propylene glycol
Span 80
Transcutol P

[a] Glycerin content $>$ 5%.
Note: Mixtures with compatible excipients may allow these to be used in lower concentrations. Limit must be determined experimentally.

Copyright © 2003 Marcel Dekker, Inc.

Table 8 European Automatic Capsule-Filling Machines for Liquid Filling of Hard Gelatin Capsules

Machine type	Number of capsules/segment	Approximate filling rate (capsules/h)
Robert Bosch GmbH		
GKF 400 L	3	10,000
GKF 800 L	6	30,000
GKF 1500 L (2 pumps)	6	60,000
Harro Hoefliger GmbH		
KFM III-I	1	3,500
KFM III	3	10,000
IMA Zanasi Division		
Z 12	2	9,000
Z 48 Plus	6	35,000
Z 85 Plus	11	60,000
MG2		
Compact	Continuous motion	4,000–35,000
Futura	Continuous motion	4,000–60,000

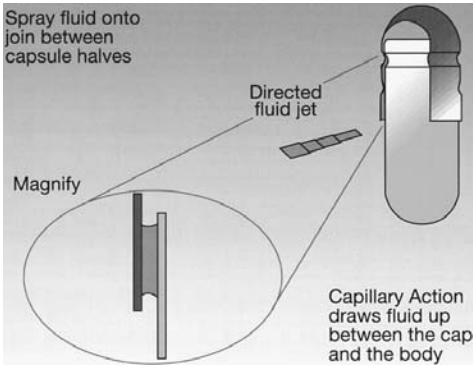

Spray fluid onto join between capsule halves
Directed fluid jet
Magnify
Capillary Action draws fluid up between the cap and the body

Figure 2 Illustration of spraying process to moisturize the space between cap and body of the capsule. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

Table 9 Stages During the Sealing of Liquid-Filled Hard Gelatin Capsules

Stage	Process
1. Moisturizing	50:50 water/ethanol mixture sprayed onto the join and capillary action draws liquid into the space between body and cap. Excess fluid removed by suction. Melting point of gelatin lowered by presence of water.
2. Warming	Application of gentle heat of approx. 45°C completes the melting over a period of about 1 min and the two gelatin layers are fused together to form a complete 360° seal.
3. Setting	Gelatin setting or hardening process is completed while the product returns to room temperature. This process is best carried out on trays.

sugel has developed a bench top machine (CFS 1000™) which is shown in Fig. 4. This machine automatically fills and seals up to 1000 capsules per hour.

Numerous companies familiar with the hard gelatin capsule banding operation have evaluated the capsule sealing technology using LEMS and over a period of time a neutral comparison of the two processes has been possible. This comparison is shown in Table 10.

Figure 3 LEMS 30 machine for sealing hard gelatin capsules. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

Figure 4 CFS 1000 capsule liquid filling and sealing machine. (See color insert.)

Table 10 Comparison of the Hard Gelatin Capsule Sealing and Banding Technologies

Aspect	Capsule sealing using Lems™	Capsule banding[a]
Installation and startup	Easy, quick	Difficult, time consuming
Machine operation	User friendly	User unfriendly
Initial capital costs	Low	High
Time for size change	~1 h	~8 h
Capsule rectification	No	Yes
Cleaning time	2–3 h	~12 h
Sealed area	Large	Small area of band
Gelatin handling	No	Yes
Current maximum machine output	30,000/h	80,000/h
Solvent exhaust	Yes	No

[a] Quali-seal™, S-100 Shionogi.

Copyright © 2003 Marcel Dekker, Inc.

VI. CONCLUSIONS

For drugs requiring modified formulations, sealed hard gelatin capsules are a viable option to soft gelatin capsules, providing the formulation scientist with an inhouse possibility during the early stages of development to rapidly prepare products for clinical trials. The process can also be readily scaled-up to production level.

REFERENCES

1. I Ghebre-Sellassie. Multiparticulate Oral Drug Delivery. New York: Marcel Dekker, 1994.
2. SE Walker, K Bedford, T Eaves. Pharmaceutical preparations in solid unit dosage form. British patent 1,572,266, 1980.
3. C McTaggart, R Wood, K Bedford, SE Walker. The evaluation of an automatic system for filling liquids into hard gelatin capsules. J Pharm Pharmacol 36:119–121, 1984.
4. A Cuiné, C Mathis, A Stamm, D. François. Das einbringen viskoser lösungen von aktivstoffen in hartgelatinekapseln. Pharm Ind 40:654–657, 1987.
5. P Ghirardi, G Catenazzo, O Mantero, GC Merotti, A Marzo. Bioavailability of digoxin in a new soluble pharmaceutical formulation in capsules. J Pharm Sci 66: 267–269, 1977.
6. W Lahr. Flüssig befüllte hartgelatinekapseln. Pharm Ztg 131:871–874, 1986.
7. R Herrmann. Bioverfügbarkeit zweier neuer nifedipin-formulierungen. Pharm Ztg 131:869–870, 1986.
8. CA Lipinski. Strategies for optimizing oral drug delivery: Consideration of drug solubility in high throughput screening of oral drug candidates. Kobe, April 19–21, 1999.
9. JR Robinson. Introduction: Semi-solid formulations for oral drug delivery. Bull Tech Gattefossé No. 89:11, 1996.
10. JM Kovarik, EA Mueller, J-B Van-Bree, W Tetzloff, K Kutz. Reduced inter- and intraindividual variability in cyclosporin pharmacokinetics from a microemulsion formulation. J Pharm Sci 83:444–446, 1994.
11. A Meinzer, F Richter, JF Vonderscher. Oil-free pharmaceutical compositions containing cyclosporin A. WO 93/20833, 1988.
12. SE Walker, JA Ganley, K Bedford, T Eaves. The filling of molten and thixotropic formulations into hard gelatin capsules. J Pharm Pharmacol 32:389–393, 1980.
13. JR Howard, PL Gould. Drug release from thermosetting fatty vehicles filled into hard gelatin capsules. Drug Dev Ind Pharm 13:1031–1045, 1987.
14. A-C Bernasconi, E Doelker, P Buri. Diffusion and erosion controlled drug release from lipid matrix formulations incorporated into hard gelatin capsules. Proc Int Symp Control Rel Bioact Mater 12:272–273, 1985.
15. AB Dennis, IW Kellaway, R Davidson. Investigation of in vitro aging on in vivo release from a prolonged release liquid filled hard gelatin capsule formulation. Proc Int Symp Control Rel Bioact Mater 15:390–391, 1988.

Copyright © 2003 Marcel Dekker, Inc.

16. Y Seta, F Higuchi, Y Kawahara, K Nishimura, R Okada. Design and preparation of captopril sustained-release dosage forms and their biopharmaceutical properties. Int J Pharm 41:245–254, 1988.
17. Y Seta, F Higushi, T Otsuka, Y Kawahara, K Nishimura, R Okada and H Koyke. Preparation and pharmacological evaluation of captopril sustained-release dosage forms using oily semisolid matrix. Int J Pharm 41:255–262, 1988.
18. Y Seta, T Otsuka, H Tokiwa, H Naganuma, Y Kawahara, K Nishimura, R Okada. Design of captopril sustained-release preparation with oily semisolid matrix intended for use in human subjects. Int J Pharm 41:263–269, 1988.
19. ET Cole. Liquid filled and sealed hard gelatin capsules. Bull Tech Gattefossé No. 92:67–77, 1999.
20. M Duerr, HU Fridolin, KD Gneuss. Entwicklung von rezepturen und verfahren zur abfüllung von flüssigen massen in hartgelatinekapseln unter produktionsbedingungen. Acta Pharm Technol 29:245–251, 1983.
21. D Cadé, ET Cole, J-Ph Mayer, F Wittwer. Liquid filled and sealed hard gelatin capsules. Acta Pharm Technol 33:97–100, 1987.
22. RA Lucas, WJ Bowtle, R Ryden. Disposition of vancomycin in healthy volunteers from oral solution and semi-solid matrix capsules. J Clin Pharm Ther 12:27–31, 1987.
23. WJ Bowtle, NJ Barker, J Wodhams. A new approach to vancomycin formulation using filling technology for semisolid matrix capsules. Pharm Technol 12:86–97, 1988.
24. C Doelker, E Doelker, P Buri, L Waginaire. The incorporation and in vitro release profile of liquid, deliquescent or unstable drugs with fusible excipients in hard gelatin capsules. Drug Dev Ind Pharm 12:1553–1565, 1986.
25. RF Jimerson. Soft gelatin capsule update. Drug Dev Ind Pharm 12:1133–1144, 1986.
26. KH Bauer. Die herstellung von hart- und weichgelatinekapseln. In: W Fahrig. UH Hofer, eds. Die Kapsel. Stuttgart: Wissenschaftliche Verlags GmbH, 1983, pp. 58–82.
27. NA Armstrong, KC James, WKL Pugh. Drug migration into soft gelatin capsule shells and its effect on in-vitro availability. J Pharm Pharmacol 36:361–365, 1984.
28. FS Hom, SA Veresh, WR Ebert. Soft gelatin capsules. II. Oxygen permeability study of capsule shells. J Pharm Sci 64 (5):851–857, 1975.
29. WJ Bowtle. Liquid filling of hard gelatin capsules: a new technology for alternative formulations. Pharm Tech Eur 10:84–90, 1998.
30. D Cadé, N Madit. Liquid filling in hard gelatin capsules—preliminary steps. Bull Tech Gattefossé No. 89:15–19, 1996.
31. CM Bond, KA Lees, JL Packington. Cephalexin: a new oral broad-spectrum antibiotic. Pharm J 205:210–214, 1970.
32. MJ Kontny, CA Mulski. Gelatin capsule brittleness as a function of relative humidity at room temperature. Int J Pharm 54:79–85, 1989.
33. M Dey, R Enever, M Kraml, DG Prue, D Smith, R Weierstall. The dissolution and bioavailability of etodolac from capsules exposed to conditions of high relative humidity and temperatures. Pharm Res 10:1295–1300, 1993.
34. Anonymous. Collaborative development of two-tier dissolution testing for gelatin capsules and gelatin-coated tablets using enzyme-containing media. Pharmacopeial Forum 24:7045–7050, 1998.

Copyright © 2003 Marcel Dekker, Inc.

35. RM Mhatre, H Malinowski, H Nguyen, MC Meyer, AB Straughn, L Lesko, RL Williams. The effects of cross-linking in gelatin capsules on the bioequivalence of acetaminophen. Pharm Res 14:3251, 1997.
36. J Brown, N Madit. ET Cole, IR Wilding, D Cadé. The effect of cross-linking on the in vivo disintegration of hard gelatin capsules. Pharm Res 15:1026–1030, 1998.
37. SM Chatham. The use of bases in semi-solid matrix formulations. STP Pharma 3: 575–582, 1987.
38. ET Cole. Liquid filled hard gelatin capsules. Pharm Technol Int Sept/Oct 1989, pp. 29–33.
39. F Wittwer. New developments in hermetic sealing of hard gelatin capsules. Pharm Manufac 2:24–27, 1985.
40. USP 23, General Information. Pharmaceutical Dosage Forms 1151, 1995, pp. 1942–1943.

Copyright © 2003 Marcel Dekker, Inc.

15
The Zydis Oral Fast-Dissolving Dosage Form

Patrick Kearney
R. P. Scherer, Swindon, England

I. INTRODUCTION

This chapter describes the Zydis lyophilized oral dosage form, which has been in commercial production since 1986 and as such represents the pioneering technology in the fast-dissolving or "fast-melt" range of solid oral dosage forms.

The primary advantage of the fast-melt dosage forms is that they do not need to be chewed because they disintegrate quickly and completely in the small amount of saliva in the mouth. This makes them easy to swallow, avoiding the need to take them with water. It is estimated that 25% of the population find it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctor, resulting in ineffective therapy. This difficulty is experienced in particular by pediatric and geriatric patients. Also, the inconvenience associated with administering standard dosage forms applies to people who are ill in bed and to those active working patients who are busy or traveling and who have no access to water. The introduction of the Zydis technology therefore addressed a significant compliance problem with solid oral dosage forms. In addition to this main application, the nature of the dosage form also makes it ideally suited for delivering drugs that are absorbed buccally.

II. HISTORY

Freeze drying, or lyophilization, has been in existence since the early 1900s [1]. A general property of aqueous freeze-dried materials is that they are readily re-

Copyright © 2003 Marcel Dekker, Inc.

constituted in water by virtue of the high porosity. Indeed, the term "lyophilization" was derived from this property. It was not until the late 1970s that this was seriously considered as a possible means of producing solid dosage forms that would "melt" on the tongue and therefore ease the administration of medicines.

The patents relating to the basic process of producing dosage forms by freeze-drying aqueous drug dispersions directly in the packaging were first filed in the early eighties [2,3]. As the technology has developed, several additional patents have been granted covering the process [4], formulation [5], and packaging [6].

III. DESCRIPTION OF THE DOSAGE FORM AND MODE OF DRUG RELEASE

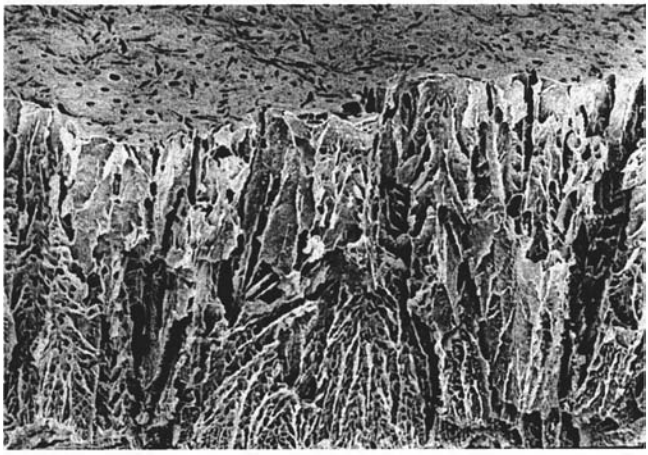
Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the characteristically high porosity produced by the freeze-drying process used in its manufacture. Figure 1 shows a scanning electron micrograph of a cross section of a Zydis formulation, and the random and extensive nature of the pores can be clearly seen. This highly porous structure allows the rapid ingress of saliva, which quickly dissolves the soluble excipients, releasing the drug particles as a suspension or solution on the tongue. The suspension is then swallowed and the drug absorbed in the normal way. Human in vivo studies, using gamma scintigraphy, have shown that even when taken without water, the component materials of the formulation uniformly disperse over the mucosa and are subsequently cleared efficiently from the buccal and esophageal region [7]. In some cases, depending on the characteristics of the drug, absorption can take place within the oral cavity.

IV. OTHER RELATED TECHNOLOGIES

A number of other fast-dissolving oral technologies have been introduced in recent years, such as Lyoc (Laboratoires L. Lafon, Maisons Alfort, France), Orasolv (CIMA Labs, Inc., Eden Prairie, MN), WOWTAB (Yamanouchi Pharma Technologies, Inc., Palo Alto, CA), and Flashtab (Ethypharm). Lyoc utilizes a freeze-drying process but differs from Zydis in that the product is frozen on the freeze-dryer shelves. To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are comparable with the loosely compressed fast-melt formulations.

Copyright © 2003 Marcel Dekker, Inc.

A



B

Figure 1 (A) Zydis dosage form and blister pack. (B) Scanning electron micrograph of cross section through a Zydis formulation.

Copyright © 2003 Marcel Dekker, Inc.

The other technologies listed utilize either dry-powder compression techniques or molding processes to produce the tablet forms, and rely on the fast disintegrating properties of the excipients to produce the spontaneous dispersion in the mouth. These processes produce tablets that are more dense and therefore significantly less porous than the Zydis form, resulting in slower disintegration times, typically 30–60 s. Fast-melt forms made by compression are significantly more friable than conventional tablets and so require special single-dose unit packaging.

V. ZYDIS FORMULATION CONSIDERATIONS

The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water-soluble structure formers. The resultant mixture is then poured into the preformed blister pockets of a laminate film and freeze-dried. The two most commonly used structural excipients are gelatin and mannitol although other suitable structure formers can be used (e.g., starches, gums, etc.) depending on the properties of the active ingredient. As a general rule, the best physical characteristics are achieved by using a mixture of a water-soluble polymer and a crystalline sugar alcohol or amino acid at a typical combined concentration of 10% w/w in the matrix solution. The polymer gives the strength and resilience while the crystalline component gives the hardness and texture.

The Zydis process is ideally suited to low-solubility drugs as these are more readily freeze-dried. For low-solubility drugs, doses up to 400 mg can be formulated in tablet sizes ranging from 8 to 18 mm. Owing to the extra volume of drug in the higher doses, overall porosity is reduced and disintegration times will be slightly slower than for the lower doses, but never usually greater than 10 s.

The maximum dose for soluble drugs is more limited and depends on the intrinsic properties of the drug, with the largest dose formulated to date being 60 mg. The usual approach to formulating larger doses of soluble drugs is to select the less soluble form, such as a free base or free acid, or to use pH-modifying excipients to minimize solubility or produce an in situ conversion to a lower-solubility form during the manufacturing process [8].

Taste is obviously important for this type of dosage form, and in most cases, it is possible to produce palatable formulations by using conventional flavors and artificial sweeteners. However, if the active has a particularly unpleasant taste, this can be overcome by using a microencapsulated form of the drug [9], or in the case of certain soluble drugs, it is possible to form low-solubility complexes with powdered ion-exchange resins [5] and so remove the drug from solution.

The preferred particle size is 90% less than 50 μm to reduce sedimentation of drug during processing and to help ensure a smooth texture in the mouth.

Copyright © 2003 Marcel Dekker, Inc.

The high porosity, typically 80%, means that the dosage form has a low intrinsic mechanical strength (0.1–0.4 Nmm^{-2}). However, the blister packaging in which the dosage form is prepared provides the necessary support and protection during the manufacturing process and subsequent handling and transportation.

VI. ZYDIS MANUFACTURING PROCESS

The commercial Zydis manufacturing process, schematically outlined in Figure 2, consists of the steps described below.

A. Preparation of Drug Suspension/Solution

A vacuum mixer is used to first prepare the aqueous solution of excipients and then to add and disperse the active ingredient by high shear homogenization. Once prepared, the solution or dispersion is transferred to a holding vessel.

B. Forming-Filling

The drug suspension is circulated from the holding vessel through a manifold supplying a series of positive displacement pumps. These pumps deliver the required volume of material along the delivery lines into the blister pockets, which are preformed in a continuous ribbon of plastic laminate.

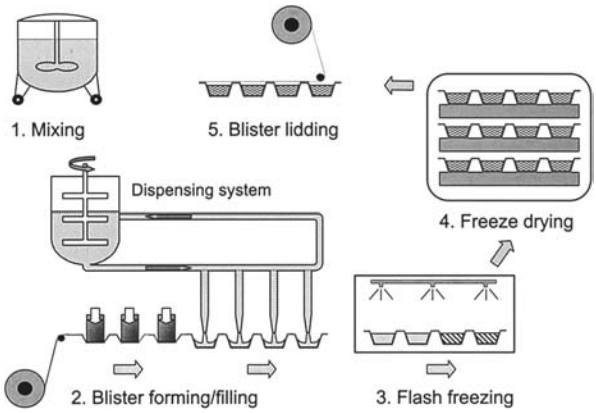


Figure 2 Schematic of the Zydis manufacturing process.

Copyright © 2003 Marcel Dekker, Inc.

C. Freezing

After the blister pockets are Filled, the blister ribbon is cut into short lengths, called "trays," which are transferred on a conveyor through the freeze tunnel. The cold nitrogen atmosphere freezes the product within minutes. This "flash" freezing "fixes" the homogeneity of the components and creates the appropriate ice crystal structure that determines the porosity of the final product. The frozen product is collected and transferred to a series of refrigerated storage cabinets to maintain it in the frozen state prior to loading into the freeze dryer.

D. Freeze Drying

The "trays" containing the frozen product are loaded onto the shelves of the freeze dryer and the ice removed by sublimation at low pressure. The dryers are characterized by a short intershelf spacing, which maximizes the product loading and accelerates the drying process. Typical drying times are on the order of 5 h.

E. Blister Lidding

The dried product is then sealed into the blister pockets by application of the lidding foil and the blister pack is then punched out to the required format.

VII. PACKAGING

Given that the Zydis blister pack confers both strength and protection to the product, it can justifiably be considered an integral part of the product, and so receives appropriate attention from an early stage in product development. The in situ freeze-drying process results in a slight degree of adhesion between the dried product and the surface of laminate and this ensures that the formulation remains fixed in the blister pocket until it is removed immediately prior to administration. This adhesion, and the natural "perfect fit" of the dose in the blister cavity, also means that the product cannot move around within the pocket, so it cannot be abraded through handling or transportation.

Owing to the low mechanical strength of the dosage form, a push-through blister lidding is not appropriate and instead the product is sealed into the blister pack using a peelable lidding foil. Removal is achieved by first peeling back the segment of foil over the pocket and then raising the tablet out of the cavity by depressing the blister.

As the dosage form is actually molded by the shape of the blister pocket, it is possible to form identification marks directly on the tablet surface by embossing the appropriate design into the base of the blister pocket [10].

Copyright © 2003 Marcel Dekker, Inc.

Unlike other freeze-drying processes, e.g., for parenterals, the drying cycle in the Zydis process does not determine the final residual moisture content of the product. Moisture levels of 2% w/w are typically achieved at the end of the cycle, but once the product is removed from the dryer it quickly reabsorbs water from the atmosphere to a level dependent on the nature of the formulation and this can vary from 3 to 8% w/w.

At ambient temperature, the lyophilized matrix can reversibly absorb higher amounts of water without adversely affecting the physical stability of the product. However, at elevated temperature and humidity, e.g., 40°C 75% RH, sufficient water can be absorbed to cause shrinkage of the product. For products developed in a PVC/PVdC blister, moisture ingress is prevented by a secondary wrapping of the blister in a paper/aluminium sachet. Other products use an aluminium blister laminate that confers complete protection from moisture.

VIII. KEY ISSUES RESOLVED DURING DEVELOPMENT OF THE TECHNOLOGY

Some key issues to be resolved during the early development of the technology were: (a) the identification of the optimal matrix formula, (b) the maintenance of dose uniformity during manufacture, (c) a high-capacity freeze-drying process, and (d) moisture-resistant packaging.

The tablet matrix had to be composed of materials that could be readily freeze-dried and also imparted sufficient strength to allow it to be neatly removed from the packaging. The selected materials also had to be compatible with a wide range of actives. Systematic screening showed that no single existing excipient had the ideal characteristics, but a suitable matrix structure was achieved by using the combination of a water-soluble polymer (e.g., gelatin) and a sugar alcohol (e.g., mannitol).

Low-concentration matrix solutions are required to ensure the rapid disintegration properties of the finished product. Such solutions naturally have low viscosity and therefore offer little resistance to the settling of suspended drug particles. Critical to the establishment of the commercial process was the ability to maintain the bulk of the suspension homogeneous while it was filled into the blister pockets. This was achieved by the design of a recirculation system with the appropriate hydrodynamics to ensure that a uniform suspension is constantly presented to the dispensing pumps throughout the filling process.

For the process to be made commercially viable, it was necessary to develop a freeze-drying process capable of rapidly drying several hundred thousand frozen tablets per load. This necessitated the design and construction of the industry's largest freeze dryers with total shelf areas in excess of 100 m^2.

Most fast-melt dosage forms are more sensitive to moisture than conven-

Copyright © 2003 Marcel Dekker, Inc.

tional compressed tablets and so need to be packaged in appropriately high-barrier materials. Aluminium blister laminates, which offer complete protection from moisture, had been available for some time but these were unsuitable for the Zydis process owing to buckling and deformation during the freezing and drying processes. This was overcome by specifically developing a laminate that, by virtue of its symmetrical structure, was not distorted during the manufacturing process.

IX. BUCCAL ABSORPTION

In most cases Zydis formulations will be bioequivalent to a well-formulated tablet or capsule. This is because with an optimized immediate-release formulation, the speed of disintegration is not generally the rate-limiting step for absorption. However, for drugs with appropriate physical chemistry, administration in a Zydis formulation can enable a significant amount of the dose to be absorbed from the buccal cavity or other areas of the "pregastric" region. Selegiline is an example of a drug that shows this effect, and Figure 3 shows plots of the plasma levels measured following administration of a 10-mg Zydis formulation and an equivalent 10-mg tablet formulation. The AUC measured for the Zydis formulation is eight times greater than that achieved with the tablet formulation. Also, the T_{max} for the Zydis form is significantly shorter. As selegiline is extensively metabolized in the liver, the result indicates the avoidance of first-pass metabolism as a result of most of the dose being absorbed in the pregastric region [11]. This made it possible to develop a 1.25-mg Zydis selegiline product with equiva-

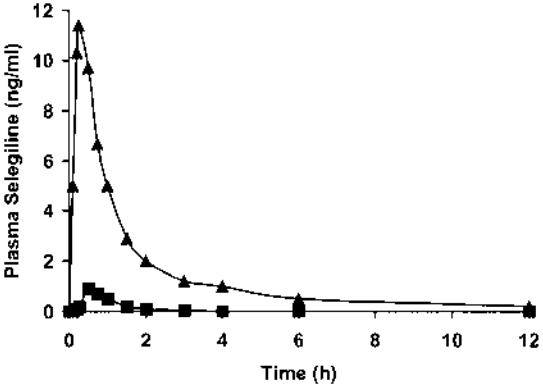


Figure 3 Selegiline concentration in plasma following oral administration of: ■, tablet 10 mg; ▲, Zydis 10 mg.

Copyright © 2003 Marcel Dekker, Inc.

lent efficacy to the 10-mg conventional tablet with the added advantage of reduced side effect due to a reduction in metabolites.

A range of other drugs have shown significant buccal absorption when given in the Zydis form including apomorphine, buspirone [12], midazolam, and timolol. The key properties that determine if a drug will exhibit this effect are:

1. Molecular weight < 500 Da
2. High aqueous solubility
3. Log P at pH 6–7, >1
4. Dose less than 20 mg

Properties 1–3 are generally accepted as those properties required for efficient uptake and transport through the mucosa. It is expected that the efficiency of pregastric absorption will be increased for lower doses of drug because larger doses will form a bolus mass, which will be taken quickly down to the stomach by the swallowing action. For smaller doses, a greater proportion of the dissolved drug will be retained in the film of saliva on the surface of the mucosa of the mouth and esophagus. This dose-related clearance rate has been shown for Zydis formulations by using gamma scintigraphy [13].

Appropriate excipients can be used to modify the mucosal absorption profile by shifting the local pH to change the drug solubility or lipid-partitioning behavior [12].

In theory, any fast-melt form could be used to deliver a buccally absorbed drug. In practice, the compressed forms may be less efficient in this regard because of their greater mass, which will tend to lead to a greater clearance rate from the absorptive surface of the buccal mucosa.

X. REGULATORY STATUS

Zydis is now well established worldwide with products registered in over 40 countries. Most have been developed as bioequivalent line extensions to existing tablet forms, and have therefore been registered on the basis of bioequivalence alone. Those like selegiline, which have a significantly different absorption profile to the tablet formulation, obviously require the filing of new clinical efficacy studies. In some cases, additional pharmacokinetic data comparing the effects of taking the Zydis form with and without water have also been included.

XI. APPLICATIONS OF THE TECHNOLOGY

Currently 13 Zydis products are manufactured for a worldwide market (Table 1). In most cases the application is the provision of an easy-to-take equivalent

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Current Zydis Products and Scherer Collaborators

Product	Compound	Company	First launch
Temesta	Lorazepam	Wyeth	1986
Seresta	Oxazepam	Wyeth	1986
Feldene	Piroxicam	Pfizer	1992
Imodium	Loperamide	Janssen	1993
Pepcid	Famotidine	Merck	1993
Claritin	Loratadine	Schering Plough	1997
Innovace	Enalapril	Merck	1998
Maxalt	Rizatriptan	Merck	1998
Zelapar	Selegiline	Elan	1998
Zofran	Ondansetron	Glaxo Wellcome	1999
Motilium	Domperidone	Janssen	1999
Zyprexa	Olanzapine	Eli Lilly	2000
Semper	Scopolamine/chlorpheniramine	Taisho	2000

of existing products to improve patient compliance and therefore aid therapy. The selegiline product (Zelapar) is the first example of those cases where the dosage form can be used to modify or enhance the bioavailability of a drug to improve clinical efficacy.

XII. FUTURE DEVELOPMENTS

It is envisaged that the primary application for the Zydis dosage from will continue to be as the more patient-friendly alternative to conventional solid dosage forms. However, a number of further opportunities are currently under evaluation relating to the more specialized area of oral mucosal absorption. These include the delivery of peptide and protein drugs and vaccines. In addition to the favorable buccal characteristics of the dosage form, from a stability and compatibility viewpoint, the freeze-drying process makes this the ideal dosage vehicle for such products.

REFERENCES

1. TA Jennings. Lyophilisation—Introduction and Basic Principles. Interpharm Press, 1999, pp. 1–13.

Copyright © 2003 Marcel Dekker, Inc.

2. GKE Gregory, DSS Ho. Pharmaceutical dosage form packages. US patent 4,305,502, 1981.
3. GKE Gregory, JM Peach, JD Du Mayne. Articles for carrying chemicals. US patent 4,371,516, 1983.
4. R Green, P Kearney. Process for preparing fast dispersing solid oral dosage form. US patent 5,976,577, 1999.
5. MC Iles, AD Atherton, NM Copping. Freeze-dried dosage forms and methods for preparing the same. US patent 5,188,825, 1993.
6. P Kearney, AR Thompson, RJ Yarwood. Method for manufacturing freeze dried dosages in a multilaminate blister pack. US patent 5,729,958, 1994.
7. N Washington, CG Wilson, JL Greaves, S Norman, JM Peach, KA Pugh. A gamma scintigraphic study of gastric coating by Expidet, tablet and liquid formulations. Int J Pharm 57:17–22, 1989.
8. RJ Yarwood, P Kearney, AR Thompson. Process for preparing solid pharmaceutical dosage forms. US patent 5,837,287, 1998.
9. L Grother, R Green, M Hall, P Kearney. Taste masking in the Zydis freeze dried dosage form. Proceedings of the 17th Pharmaceutical Technology Conference, Dublin, 1998, pp. 239–250.
10. AR Thompson, RJ Yarwood, P Kearney. Method of identifying freeze-dried dosage forms. US patent 5,457,895, 1995.
11. A Clarke, F Brewer, ES Johnson, EA Kelly. Proceedings of the 122nd Annual Meeting of the American Neurological Association, 1997, M69.
12. R Green, M Hall, F Brewer, J Lacy, N Mallard, S Rowkins, S Taylor, A Clarke, P Kearney. Pharmaceutical aspects relating to pre-gastric absorption from the Zydis dosage form. Proceedings of the 17th Pharmaceutical Technology Conference, Dublin, 1998, pp. 10–21.
13. CG Wilson, N Washington, JL Peach, GR Murray, J Kennerley. The behaviour of a fast-dissolving dosage form (Expidet) followed by gamma-scintigraphy. Int J Pharm 40:119–123, 1987.

Copyright © 2003 Marcel Dekker, Inc.

16

OraSolv and DuraSolv: Efficient Technologies for the Production of Orally Disintegrating Tablets

S. Indiran Pather, Rajendra K. Khankari, and Derek V. Moe
CIMA LABS Inc., Brooklyn Park, Minnesota, U.S.A.

I. INTRODUCTION

This chapter describes the intraorally disintegrating or dissolving tablets OraSolv®, and the second-generation platform, DuraSolv®, developed and manufactured by CIMA LABS Inc. The taste of the active ingredient in these products is masked by the use of an appropriate coating over the drug particles in conjunction with effective flavoring agents and an artificial sweetener. They are designed to facilitate the administration of medication to patients who experience difficulty in swallowing (dysphagia) and for the convenience of all patients since the products may be administered at any time, without the need for water or other liquid to aid swallowing. Additionally, these technologies help pharmaceutical companies to extend the life cycle of their products and to differentiate them in the marketplace. The technologies for the formulation, production, and packaging of the tablets are covered by several patents as indicated below.

II. HISTORICAL DEVELOPMENT

Chewable tablets have historically been provided to those who cannot swallow tablets easily. The disadvantage to the patient was the chalky taste that such preparations often had. In addition, if unpleasant tasting drugs were coated to reduce taste perception, the resulting particles were frequently large and felt gritty

Copyright © 2003 Marcel Dekker, Inc.

during chewing. The process of chewing also tended to damage the coating, thus compromising the taste-masking attributes.

Soluble tablets, which were predissolved in a glass of water before consumption by the patient, overcame some of these issues. However, taste masking was more difficult to achieve and, in addition, it was often difficult to fulfill the preferred requirement that all components of the tablet be water soluble. Insoluble lubricants, such as magnesium stearate, resulted in a "scum" floating on the surface of the solution or they left a "dirty" residue on the sides of the container. Orally disintegrating tablets overcame these problems. In this sense, CIMA LABS' Autolution™ technology for solution tablets can be seen as the predecessor technology.

III. DESCRIPTION OF THE TECHNOLOGY

A key attribute of the OraSolv technology is the fact that saliva causes the relatively soft tablet to rapidly disintegrate in the mouth. The resulting constituents partially dissolve and are swallowed with the saliva. Since no chewing is necessary, the potential for fracture of the coating is decreased. An essential feature is the presence of an effervescent couple that acts as a disintegrating agent while also assisting with taste masking and providing a pleasant "fizzing" sensation in the mouth. The DuraSolv tablets, on the other hand, dissolve rapidly without pronounced disintegration. This is due to the presence of a large proportion of fast-dissolving excipients in fine particle form. This process is aided by the incorporation of wicking agents that rapidly introduce the solvent (saliva) into the body of the tablet. Swelling disintegrants, if used at all, are kept to a minimum. The overall effect of these formulation approaches is a product that appears to melt in the mouth and is not gritty during consumption. Small amounts of effervescence may, optionally, be incorporated to assist taste masking but the concentrations should not be high enough to promote rapid disintegration.

IV. RESEARCH AND DEVELOPMENT

A. Rationale for Formulating Quick-Dissolving Tablets

Dosage forms exist to optimize the *delivery* of a pharmaceutical active to its site of action. To this end, various sophisticated and often ingenious delivery systems have been developed. Attainment of suitable blood concentration/time profiles in controlled studies is regarded as validation of the effectiveness of the specialized dosage form. However, it should be remembered that "delivery" also encompasses the role of the patient actually consuming the medication in an uncontrolled setting. There is, thus, the need for patient-friendly, convenient dosage

Copyright © 2003 Marcel Dekker, Inc.

forms. Patient convenience leads to compliance with the prescribed dosing regimen and, as a consequence, to enhanced therapy. Compliance has become a major problem, particularly for children and for senior citizens. The need for a patient-friendly dosage form may be satisfied by a quick-dissolving intraoral tablet that has a pleasant taste and mouth feel, and can be taken at any time or place without regard to the availability of water or the need to swallow a large mass of material as a unit.

B. Formulation and Manufacturing Technology

In this technical section, a brief overview is provided of the formulation, production, and packaging of OraSolv and DuraSolv, the two technologies that have been patented and commercialized by CIMA LABS Inc. The OraSolv product is a soft tablet that needs special packaging. The DuraSolv tablet is a comparatively harder tablet which, nevertheless, is able to rapidly dissolve in the mouth. The advantage of the latter is that it can be cost-effectively packaged in conventional containers, such as bottles.

1. OraSolv

The ideal orally disintegrating tablet formulation disintegrates quickly in the oral cavity, releases 100% of the active ingredient in the gastrointestinal tract, and has a pleasant taste and creamy mouth feel [1]. The fast disintegration is achieved by compressing water-soluble excipients using a lower range of compression forces than are normally used in tableting. The time for the disintegration of OraSolv tablets within the oral cavity varies from 6 s to 40 s, depending largely on tablet size and the compression force (within the lower range) that was used to form the tablet. The low compression force leads to high tablet porosity which, in turn, accelerates the rate of disintegration of the tablet and dissolution of the water-soluble excipients. Disintegrating agents further facilitate the process, an effervescent couple being used as a water-soluble disintegrating agent [2]. Thus, the OraSolv tablet comprises the following components: taste-masked active(s), filler, sweetener, disintegrating agent, lubricant, glidant, flavor, and coloring agent.

The active ingredients can be taste-masked using a variety of techniques such as fluid bed coating, microencapsulation, or spray congealing. The type of taste-masking system used is dictated by the physicochemical properties of the active ingredient and its physical form. For example, an active ingredient with a mean particle diameter of 200–300 μm may lend itself to direct particle coating. A good orally disintegrating tablet imparts no unpleasant taste. This requirement can be met with adequate coating that limits drug dissolution to an insignificant level within the oral cavity. To display an acceptable bioavailability, however,

Copyright © 2003 Marcel Dekker, Inc.

dissolution within the gastrointestinal tract should be rapid and complete. Consequently, the taste-masking process is a balancing act between allowing insignificant dissolution in the oral cavity and achieving maximum dissolution distal to the oral cavity. When utilizing particle coating for taste masking, one may incorporate polymers that are conventionally used for sustained-release coating. From the array of coating polymers available, the appropriate combination should be used in the correct proportions to attain this balance.

The tablets are manufactured by a direct compression technique using conventional blending equipment and high-speed tablet presses. Because the OraSolv tablets are produced at low compression forces, they are soft and friable. To reduce handling of the tablets, the tableting and packaging processes are integrated [3,4] and a specially designed package [5] is used. The packaging system consists of a robot that picks up and places the tablets in dome-shaped depressions in aluminum foil. A layer of top foil is heat-sealed over the bottom foil. The integrated manufacturing line is equipped with a printing assembly that enables each blister card to be printed individually during the manufacturing process. The automated system then cuts the foil into cards of, usually, six tablets. A robot eye detects depressions that do not contain tablets and rejects these cards. The operator may also observe unfilled cards on a monitor.

The specially designed package and processing system, referred to as PakSolv™, protects the OraSolv tablets from breaking and attrition during the rigors of shipping. In particular, the dome-shaped depressions limit the vertical movement of the tablet within the package since the diameter of the lower portion of the dome is too narrow to accommodate the tablet. Thus the tablet remains in the upper part of the dome adjacent to the top foil. This is in contrast to a regular blister package in which the sides of the depression are vertical and the bottom is flat, allowing a greater range of vertical movement. PakSolv also offers light, moisture, and child resistance. Moisture resistance is important when packaging an effervescent formulation or moisture-sensitive drugs. A typical PakSolv blister package is shown in Figure 1.

2. DuraSolv

DuraSolv is Cima's second-generation fast-dissolving tablet technology. This technology provides robust yet quick-dissolving tablets. Like OraSolv, the DuraSolv tablets consist of water-soluble excipients and are manufactured using direct compression techniques. However, DuraSolv utilizes nondirectly compressible fillers in fine particle form [6,7]. These fillers have a high surface area, which increases their dissolution rate. The incorporation of a high proportion of such fillers causes the tablet to "melt" or dissolve, rather than disintegrate. Wicking agents assist the entry of water into the body of the tablet, whereas swelling disintegrants are avoided or used in small proportions. Since extensive disintegra-

Copyright © 2003 Marcel Dekker, Inc.

Figure 1 Typical PakSolv package.

tion is to be avoided, only small amounts of effervescent agents may be incorporated, if they are to be included at all. The limited disintegration contributes to the nongritty mouth feel conferred on the product by the use of fine-particle fillers. The increased dissolution rate of the soluble, fine-particle filler compensates for the reduction in tablet porosity due to the use of higher compression forces (relative to the OraSolv products). The manufacturing process utilizes conventional blenders and high-speed tablet presses. DuraSolv tablets are robust and conventional packaging equipment can be used to package them into bottles. The product may also be packaged into blisters or pouches, if desired.

Commercial products manufactured according to CIMA LABS' technologies are listed in Table 1. Several additional products are in various stages of development or registration.

C. Shipping Tests

To illustrate the robustness of the OraSolv-Paksolv combination, a series of shipping tests have been conducted by CIMA LABS. One of these tests, which involved transcontinental shipping, will be described. Five-eighths-inch OraSolv tablets that were debossed on one side were shipped from Minneapolis to Prague in the Czech Republic (December 1997–January 1998). U.S. tractor-trailer transport, an ocean voyage, European tractor-trailer road transportation, and interim storage were involved.

The tablets were packaged in cards of six, with four cards per carton. The

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Currently Marketed Intraorally Disintegrating Tablets Manufactured by CIMA LABS Inc.

Product	Active ingredients
Tempra* FirsTabs	Acetominophen 160 mg
Triaminic® Softchews™ Cold and Allergy	Pseudoephedrine HCl 15 mg, chlorpheniramine maleate 1 mg
Triaminic® Softchews™ Cold and Cough	Pseudoephedrine HCl 15 mg, dextromethorphan HBr monohydrate 5 mg, chlorpheniramine maleate 1 mg
Triaminic® Softchews™ Throat Pain and Cough	Acetominophen 160 mg, pseudoephedrine HCl 15 mg, dextromethorphan HBr monohydrate 5 mg
Triaminic® Softchews™ Cough	Dextromethorphan HBr monohydrate 7.5 mg
Triaminic® Softchews™ allergy sinus + headache	Pseudoephedrine HCl 15 mg, acetominophen 160 mg
Triaminic® Softchews™ allergy congestion	Pseudoephedrine HCl 15 mg
NuLev™	Hyoscyamine 0.125 mg
Zomig-ZMT™ 2.5 mg	Zolmitriptan 2.5 mg
Zomig-ZMT® 5 mg	Zolmitriptan 5 mg
Remeron® SolTab™	Mirtazipine 15 mg
Remeron® SolTab™	Mirtazipine 30 mg
Remeron® SolTab™	Mirtazipine 45 mg

shipping cases had 24 cartons per case. The shipping cases were palletized on two standard stretch-wrapped pallets with 120 cases per pallet. The cases were packed in six layers with 20 cases per layer. The total number of tablets shipped thus equals $6 \times 4 \times 24 \times 120 \times 2 = 138{,}240$. Using statistical sampling methods, 3648 tablets were removed from the pallets and observed for deterioration in their physical condition.

The tablets were rated on a scale of 0 to 3 using predetermined criteria as described in Table 2. The rating scale was developed prior to the test and the scores were documented by means of photographs kept on record at CIMA LABS. The results are shown in Table 3 and confirm that the OraSolv tablets in their special packaging were able to withstand the rigors of shipping.

D. Organoleptic Tests

In this section, two tests will be described: one in which an OraSolv tablet is compared to a conventional tablet with respect to taste and subject perceptions of ease of use. In the second test, an OraSolv product is compared to a quick-

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Tablet-Rating System for CIMA LABS Inc. Shipping Tests

Evaluation	Score
No dust	0
Little dust	1
Moderate dust	2
Major dust	3
Chipped or broken tablets	3

dissolving, freeze-dried wafer. The studies were conducted by Bases, a company specializing in the conduct of consumer preference and taste tests.

1. OraSolv Versus Standard Tablet

In this test, an OraSolv 20-mg famotidine tablet was compared to a standard, commercial famotidine tablet (Pepcid® 20 mg). The concept of a fast-dissolving tablet and the method of its use were explained to the subjects. Information regarding the standard tablet was also given to the subjects, using the product labeling as the information source. A protomonadic design was followed in the dosing of the 206 subjects.

The subjects rated the products by means of their agreement, or disagreement, with a series of statements with reference to each product. The results are summarized in Table 4, in which the overall preference scores are reflected, and in Table 5, in which a number of subjective ratings are presented. Table 4 shows that 3 times as many subjects preferred the OraSolv tablet compared to the standard tablet. Table 5 shows that a statistically significant number of subjects thought that the OraSolv tablet was convenient to use and was a unique way of taking medication. After using the product, the subjects' perception was that it dissolves quickly and that it did not require water to take. These perceptions were significantly different compared to those for the swallowed tablet. The subjects

Table 3 Results of International Shipping Test

Factor	Percentage rating
Dust level 0	98.3
Dust level 1	1.7
Chipped or broken tablets	0

Copyright © 2003 Marcel Dekker, Inc.

Table 4 OraSolv Versus Standard Famotidine Tablet Preference Ratings

Product preference	Respondents (%)
Preferred OraSolv tablet	75
Preferred standard tablet	24
Liked both equally	1

perceived the OraSolv tablet to be as safe as the standard tablet (no significant difference).

2. OraSolv versus Zydis

In another test, OraSolv and Zydis® formulations each containing 6.25 mg of phenylpropanolamine and 1 mg of brompheniramine maleate with a grape flavor were compared. The Zydis formulation is sold under the trade name Dimetapp® Cold and Allergy tablets (since discontinued). The testing involved 450 interviews of children (aged 6–12 years) and adults. The children were interviewed in 21 U.S. cities while the adults were interviewed in eight U.S. cities. A monadic approach was used; i.e., each subject tested only one product. The perceptions of the subjects with respect to the length of time it took for the tablets to melt in the mouth and the taste of the respective products as well as an overall preference for the products were determined. As in the previously described test, the subjects were given a series of statements for each section of the test and had to indicate with which one they identified.

The results of the test measuring melting-time perceptions are shown in

Table 5 OraSolv Versus Standard Famotidine Tablet Attribute Ratings

Description	Swallowable tablet (A)	OraSolv tablet (B)
Is safe to use	88	89
Is convenient to use	74	97*
Is a unique way of taking medication	54	90*
Dissolves quickly	52	97*
Does not require water to take it	27	92*
Total respondents	204	202

* Significant difference at the 90% confidence level or greater.

Copyright © 2003 Marcel Dekker, Inc.

Table 6 OraSolv Versus Zydis: Length of Time for Tablet to Melt

	Children (%)		Adults (%)	
	OraSolv (A)	Zydis (B)	OraSolv (C)	Zydis (D)
Too long	9	3	5	4
Just the right amount of time	71*	57	80	85
Melt too quickly	16	37*	14	10
Don't know	4	3	1	1

* Significant difference at the 90% confidence level or greater.

Table 6. A significantly greater number of children felt that the OraSolv product melted in just the right amount of time while a significantly greater number of children felt that the Zydis product melted too quickly. The adults did not perceive a difference. It is important to remember that it is the perceptions of the subjects that was determined in these tests. The Zydis product is a freeze-dried wafer and, in keeping with the nature of the product, any objective testing in a laboratory will show that it dissolves more rapidly than the OraSolv product. Yet, the adults did not perceive a difference. In a world where people are conditioned with the idea of "faster is better," it is surprising that the children felt that the Zydis product melted too quickly. The solid form of the freeze-dried wafer breaks down almost instantaneously when placed in the mouth. While the OraSolv tablet disintegrates much faster than a conventional tablet, it is, nevertheless, a compressed tablet and its disintegration time can be longer than that of the Zydis formulation. It is possible that the children did not like the "suddenness" of the Zydis reaction.

A significantly greater number of adults and children liked the OraSolv taste whereas a significantly greater number of subjects in each age group stated that they hated the Zydis taste (Table 7). A significantly greater number of children were also not sure whether they liked or disliked the Zydis taste.

The OraSolv tablet is manufactured using drug particles that are coated with a material that prevents immediate dissolution of the drug (see above). As a result, the drug does not dissolve appreciably in the mouth and therefore the taste is not perceived. In contrast to this, the freeze-drying process by which the Zydis product is made [8] does not easily incorporate a similar coating process. Both products contain a grape flavor which, in general, can be overwhelmed if the drugs have a very potent taste. With the OraSolv formulation, it is possible to taste only a very small fraction of the dose (the portion that dissolves) and this taste is masked with flavor. On the other hand, the Zydis formulation attempts to disguise the taste of a major portion of the drugs (since a large amount may dissolve and can contact the taste buds). On the other hand, the speed with which

Copyright © 2003 Marcel Dekker, Inc.

Table 7 OraSolv Versus Zydis: Intensity of Liking or Disliking Taste

	Children (%)		Adults (%)	
	OraSolv (A)	Zydis (B)	OraSolv (C)	Zydis (D)
I liked it	96*	72	84*	70
Not sure	1	15*	6	4
I hated it	3	12*	10	26*

* Significant difference at the 90% confidence level or greater.

the wafer dissolves may allow faster swallowing and removal from the taste zone. The results of the test indicate that the subjects perceived the former (OraSolv) method to be more effective in disguising the taste of this drug combination.

With respect to their overall perceptions of the products, it is clear from the data that both products were liked by the subjects. However, a significantly greater number of adults and children preferred the OraSolv product and a significantly greater number of adults stated that they hated the Zydis product (Table 8). In addition, a significantly greater number of children were unsure about their overall view of the Zydis tablet. It is clear that the better taste masking of the OraSolv product was preferred by the subjects and, unexpectedly, that the faster melting of the Zydis product was not necessarily preferred by the subjects.

E. Pharmacokinetic Tests on OraSolv

As mentioned earlier, OraSolv formulations are designed for convenience of administration, not for faster drug absorption. The coated drug particles are swallowed together with the excipient powder and dissolved excipients (and possibly a minor portion of dissolved drug). The coating around the drug-containing particles dissolves distal to the oral cavity, thereby releasing the drug for absorption.

Table 8 OraSolv Versus Zydis: Intensity of Liking Tablet Overall

	Children (%)		Adults (%)	
	OraSolv (A)	Zydis (B)	OraSolv (C)	Zydis (D)
I liked it	90*	72	87*	75
Not sure	6	19*	10	9
I hated it	4	9	3	16*

* Significant difference at the 90% confidence level or greater.

Copyright © 2003 Marcel Dekker, Inc.

Given that the drug's pharmacokinetics after OraSolv administration are not intended to be different from that observed after administration of a conventional dosage form, the OraSolv formulation may be used to substitute the latter. It then becomes incumbent on the marketer to show bioequivalence to a marketed product. Several studies have shown this to be the case. A brief description of a clinical study with pseudoephedrine follows.

A randomized, single-dose, three-way crossover study was performed to compare the bioavailability of pseudoephedrine hydrochloride, respectively, from an OraSolv formulation, Sudafed® tablets, and Children's Sudafed Liquid. The dose was either one tablet or 5 mL of liquid, thus providing 30 mg of drug in each case. After an overnight fast, each of the six adult male volunteers was given one of the formulations according to a randomization schedule. After 7-day washout periods, the alternate doses were administered. Blood samples were drawn at predetermined times for 12 h postdosing. The blood was centrifuged and the plasma separated and frozen until assayed by GC/MS. The limit of quantification for the validated assay method was 10 ng/mL. The mean plasma levels versus time plots are shown in Figure 2 and a summary of the pharmacokinetic

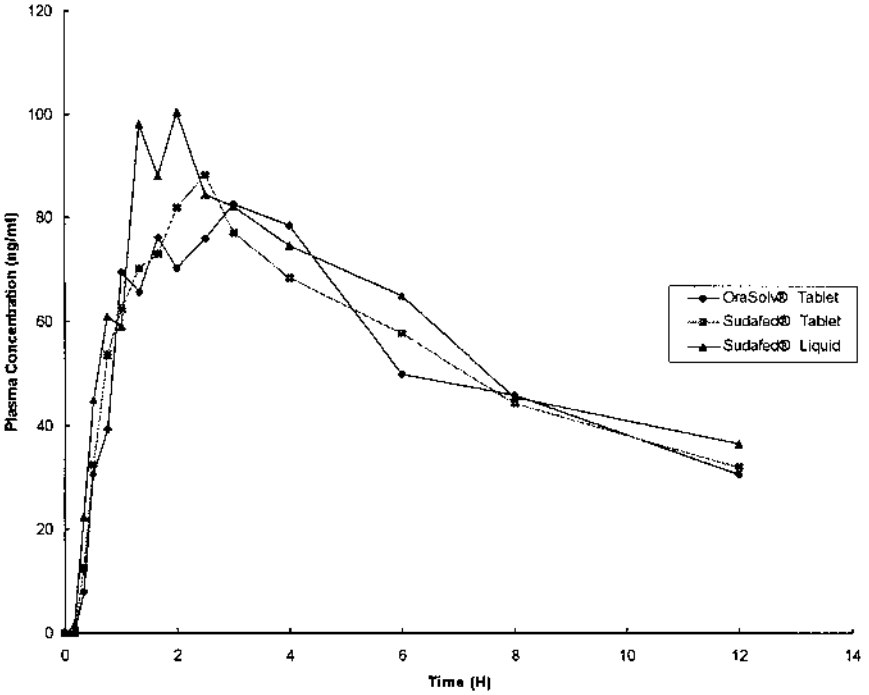


Figure 2 Comparative pseudoephedrine bioavailability.

Copyright © 2003 Marcel Dekker, Inc.

Table 9 Pseudoephedrine Pharmacokinetic Parameters for OraSolv and Sudafed Tablets

	OraSolv	Sudafed
C_{max} (±SD) (ng/mL)	94.7 (17.1)	94.5 (26.2)
T_{max} (±SD) (H)	2.07 (1.2)	2.03 (0.6)
$AUC_{0\text{-}Inf}$ (±SD) (ng*H/mL)	948.3 (328.0)	989.2 (307.7)

parameters for OraSolv and Sudafed tablets is provided in Table 9. There was no significant difference between the respective parameters for the two formulations ($p > 0.05$). These results indicate that the OraSolv formulation of pseudoephedrine is bioequivalent to Sudafed tablets.

V. TECHNOLOGY POSITION/COMPETITIVE ADVANTAGE

Some alternate orally disintegrating technologies are listed in Table 10. The Zydis product is a freeze-dried wafer consisting of a porous matrix and is, consequently, extremely soft [8]. The technology was originally developed at Wyeth [9] and improved at RP Scherer, for example by improving the taste of the product [10]. The specialized packaging needs of this dosage form are accommodated by an inner strip packing for protection against crushing and an outer foil pouch for moisture protection. The purported advantage of this technology is the extremely rapid disintegration and dissolution of the wafers. Since the product is freeze-dried, the drug is more difficult to taste mask.

The Flash Dose® (Fuisz Technologies) utilizes their patented Shearform™ technology. Flash flow processing is used to form the shearform matrix and this matrix and drug is compressed to form the tablet [11]. In the preferred embodiment, the drug is part of the matrix. In another form of this technology, the active ingredient is incorporated in a saccharide-based crystalline structure and this is

Table 10 Some Alternate Orally Disintegrating Tablet Technologies

Technology	Company	Key attributes
Zydis	RP Scherer	Freeze-dried wafers
Flash Dose	Fuisz/Biovail	Saccharides—"floss"—complex crystals
Wowtab	Yamanouchi	High- and low-moldability saccharides
Flashtab	Prographarm	Special combinations of direct compression ingredients and disintegrants

Copyright © 2003 Marcel Dekker, Inc.

tamped into a mold and cured to form the final dosing units [12]. Low compression forces are used to form this unit, which distinguishes it from a conventional compressed tablet. A detailed description of the shearform process of forming a monodispersed, microcrystalline sugar is given in another patent [13]. Certain improvements are described in additional patents [14,15]. The latter reference describes a sucrose floss, similar to candy floss, which forms the matrix of the tablets.

The Wowtab® technology introduced by Yamanouchi Pharma Technologies uses a solution of a high-moldability saccharide (a saccharide that produces a hard compact) to granulate a low-moldability saccharide (poorly compressible saccharide) [16]. The result is a tablet of sufficient hardness that, nevertheless, disintegrates rapidly. The patent claims that compaction of a physical mixture of the two types of saccharides does not produce the same result.

The Flashtab® technology of Prographarm appears to use conventional tableting ingredients. The special combination of disintegrating agents (such as carboxymethyl cellulose) with a swelling agent such as modified starch and directly compressible fillers results in a rapidly disintegrating tablet with high mechanical strength [17].

While several technologies have been described, none of them, with the notable exception of Zydis, have been extensively commercialized. Indeed, the Zydis technology at present enjoys the highest sales of all orally disintegrating technologies.

VI. FUTURE DIRECTIONS

Research at CIMA LABS, in this area of pharmaceutical endeavor, currently takes three directions:

1. Development of improved technologies for taste masking
2. Enhancements of the existing OraSolv and DuraSolv technologies
3. New approaches to orally disintegrating dosage forms

These efforts are being made in an attempt to continually improve the product presentations and to overcome challenges presented by specific active ingredients encountered.

REFERENCES

1. W Habib, R Khankari, J Hontz. Fast-dissolve drug delivery systems. Crit Rev Ther Drug Carr Syst 17:61–72, 2000.

Copyright © 2003 Marcel Dekker, Inc.

2. F Wehling, S Schuele, N Madamala. Effervescent dosage form with microparticles. US patent 5,178,878, 1993.
3. J Amborn, V Tiger. Apparatus for handling and packaging friable tablets. US patent 6,269,615, 2001.
4. J Amborn, V Tiger. Apparatus for handling and packaging friable tablets. US patent 6,311,462, 2001.
5. LD Katzner, B Jones, J Khattar, J Kosewick. Blister package and packaged tablet. US patent 6,155,423, 2000.
6. RK Khankari, J Hontz, SJ Chastain, L Katzner. Rapidly dissolving robust dosage form. US patent 6,024,981, 2000.
7. RK Khankari, J Hontz, SJ Chastain, L Katzner. Rapidly dissolving robust dosage form. US patent 6,221,392, 2001.
8. H Seager. Drug-delivery products and the Zydis fast-dissolving dosage form. J Pharm Pharmacol 50:375–382, 1998.
9. GKE Gregory, JM Peach, JD Du-Mayne. Articles for carrying chemicals. US patent 4,371,1516, 1983.
10. RJ Yarwood, P Kearney, AR Thompson. Process for preparing solid pharmaceutical dosage forms. US patent 5,738,875, 1998.
11. RC Fuisz, SR Cherukuri. Process and apparatus for making tablets and tablets made therefrom. US patent 5,654,003, 1997.
12. GL Myers, GE Battist, RC Fuisz. Process and apparatus for making rapidly dissolving dosage units and product therefrom. US patent 5,866,163, 1999.
13. RC Fuisz, GE Battist, GL Myers. Method of making crystalline sugar and products resulting therefrom. US patent 5,597,416, 1997.
14. TK Misra, JW Currington, SP Kamath, PP Sanghvi, JR Sisak, MG Raiden. Fast-dissolving comestible units formed under high-speed/light-pressure conditions. US patent 5,869,098, 1999.
15. SR Cherukuri, GL Myers, GE Battist, RC Fuisz. Process for forming quickly dispersing comestible unit and product therefrom. US patent 5,587,172, 1996.
16. T Mizumoto, Y Masuda, M Fukui. Intrabuccally dissolving compressed moldings and production process thereof. US patent 5,576,014, 1996.
17. G Cousin, E Bruna, E Gendrot. Rapidly disintegratable multiparticular tablet. US patent 5,464,632, 1995.

Copyright © 2003 Marcel Dekker, Inc.

17
Colonic Drug Delivery

Clive G. Wilson
Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland

I. INTRODUCTION

Targeted delivery of drugs to the colon is usually to achieve one or more of four objectives. The desired outcomes can be sustained delivery (a) to reduce dosing frequency; (b) to delay delivery to the colon to achieve high local concentrations in the treatment of diseases of the distal gut; (c) to delay delivery to a time appropriate to treat acute phases of disease (chronotherapy); and finally, (d) to deliver to a region that is less hostile metabolically, e.g., to facilitate absorption of acid and enzymatically labile materials, especially peptides. Further commercial benefits are the extension of patent protection and the ability to promote new claims centered on the provision of patient benefits such as the optimization of dosing frequency.

If a colonic drug delivery system functioned perfectly it would not release drug in the upper and midgastrointestinal tract, but initiate delivery of its contents at the beginning of the large bowel where conditions are most favorable for drug dispersion and absorption. When a colonic drug delivery system is being developed, it should be borne in mind that the surface area is less and the permeability characteristics are quite different in this region of the gastrointestinal tract compared to the upper and midgastrointestinal tract, leading in many cases to slow or even negligible drug flux across the colonic mucosa. In addition, the bacteria present in the colon may cause significant loss by degradation of the active moiety. To appreciate the problems and possibilities of utilizing colonic absorption, the physiological and anatomical aspects of this region of the gastrointestinal tract need to be considered.

Copyright © 2003 Marcel Dekker, Inc.

II. FUNCTION OF THE COLON: THE IMPACT ON DRUG DELIVERY

The large intestine is principally responsible for the conservation of water and electrolytes, particularly sodium chloride, whose removal facilitates the formation of a solid stool. The structure is easily discriminated from that of the small intestine as the lumen is larger and less convoluted. The major regions of the colon are illustrated in Figure 1. The transverse colon is folded in front of the ascending and descending arms. The splenic flexure will generally prevent exposure to the transverse colon following rectal administration. From the middle of the ascending colon consolidation of luminal contents occurs into a mass that gradually becomes more homogeneous and viscous. By the time the luminal contents have reached the descending colon, the mass is too solid to allow drug dispersion from a delayed-release formulation.

Current studies indicate that the distal transverse colon functions as a conduit, driving material into the descending and sigmoid colon for storage. Studies conducted in patients to measure the relative residence times of materials at steady state show that the contents are divided two-thirds into the ascending or right colon and one-third in the descending colon[1]. This difference is exaggerated in left-sided colitis to 9:1, which may explain why management is difficult

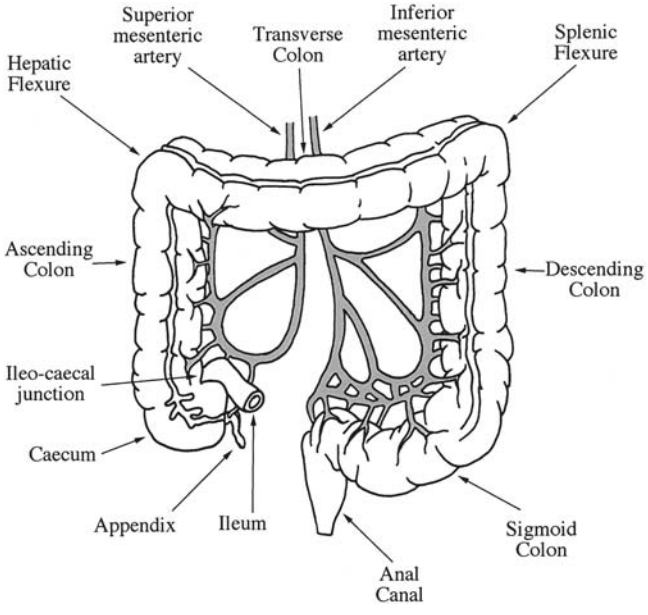


Figure 1 Main features of the colon (Adapted from Ref. [6].)

Copyright © 2003 Marcel Dekker, Inc.

in active disease [2]. The change in distribution in left-sided colitis is caused by the greater availability of water.

The interior surface differs from that of small intestine by having less surface area (no villi), the presence of plecal folds, and movement that is sluggish and largely propulsive. The structure and inhomogeneity of the contents causes a separation according to particle size: consolidation starts with lumps of debris pushed ahead of the finer particulates in the liquid phase. In drug delivery this behavior results in the separation of microparticulates and matrix systems; the finer particulates may be trapped in the folds and their retention increased.

III. TRIGGERS FOR DRUG DELIVERY

Previous studies utilizing the technique of scintigraphy have shown that small intestinal transit times in humans are relatively consistent, irrespective of the nature of the dosage form (particulate or monolith). Small intestinal transit is usually determined to be between 3 and 4 h (emptying from the stomach to arrival at the ileocecal junction) although shorter transit times are not unusual, particularly in individuals who regularly engage in high-intensity sport.

The emptying from the stomach may, however, be unpredictable, since it is dependent on the timing of the housekeeper sequence. This leads to marked differences in the time of exposure to acidic conditions (pH 1.5–2.5) in the fasted state. In the fed state, the pH can rise to between 4 and 5 and the sieving action of the pylorus will favor retention of larger objects such as enteric-coated tablets. Since entry into the duodenum provides a sharp pH rise, this change can be used to trigger the dissolution of acidic polymers used as coatings or matrices. Thickness of the coating then provides the basis for a process allowing initiation of release at an appropriate point in the intestine. Early attempts to modify the point of release by thickening the coat were successful and used to facilitate cecal targeting of drugs such as the 5-amino salicylates (5-ASA). A similar principle was used in studies designed to modulate delivery from a Pulsincap device [3]. This system utilized two triggers: the first initiated by emptying into the small intestine and the second, a swelling hydrogel cap that ejected from the base at a predetermined time governed by the length of plug and recession into the capsule body. However, an additional two triggers are available: the cecal metabolism, which provides the opportunity for reductive and glycosidic cleavage, and the low pH produced by the bacterial fermentation of soluble polymers.

IV. ROLE OF CECAL FERMENTATION

The cecal bacteria in the right side of the colon largely control the characteristics of the lumen. Complex carbohydrates are fermented by the bacteria to small-

Copyright © 2003 Marcel Dekker, Inc.

chain fatty acids and carbon dioxide, the gas traveling to the transverse colon and being expelled through the lungs. The average bacterial load of the colon has been estimated at just over 200 g (equivalent to approximately 35 g dry weight). Water available for dissolution is maximal in the ascending colon and 1.5–2 L enter from the terminal small intestine each day. The amount of water present varies, being maximal in the period 4–8 h after ingestion of a meal. In the morning, the colon is often empty, and any material remaining in the ascending colon is slowly cleared. In the upright position, the gas produced by fermentation travels to the transverse colon and may limit access of the contents to water. It would be expected that the low water–high gas environment of the transverse colon limits dissolution of materials. It also limits ingress of water into impermeable devices.

In the descending colon, devices become impacted into the 300 g of fecal contents. The surrounding material limits diffusion and provides a nonabsorbing reservoir. Therefore, unless the contents are cleared, there will be no absorption in this region.

From these comments, it can be seen that targeted delivery to the large bowel should be directed toward the proximal colon. The ascending colon provides some water for dissolution. In addition, contents at the base of the colon will be stirred by the arrival of additional fluids from the gut as meals and accompanying secretions. This area also provides two cues that can be used for targeting: the change in pH and the unique nonmammalian metabolic profile provided by cecal bacteria.

V. DISEASE AND THE COLONIC ENVIRONMENT

As in all drug formulation development, the impact of the disease process is sometimes forgotten by the pharmaceutical scientist, with the outcome that performance is not optimal [4]. All the specific approaches so far mentioned rely on the concept that enzymes produced by colonic microflora provide the trigger for specific delivery of fermentable coatings, anti-inflammatory azobond drugs, and other prodrugs to the cecum. An old observation by Carrette and colleagues in 1995 should temper undue enthusiasm [5]. Carrette and co-workers demonstrated that in patients with active Crohn's disease, the metabolic activity of digestive flora (assessed on the activity of fecal glycosidases) was decreased [5]. Azoreductase activity in feces of 14 patients with active Crohn's disease was 20% of that of healthy subjects and similarly, beta-D-glucosidase and beta-D-glucuronidase activities in fecal homogenates incubated under anaerobic conditions were also decreased in patients [5]. These data probably reflect large-bowel hypermotility and the associated diarrhea, leading to lower bacterial mass in the colon and might contribute to the therapeutic failure of targeting mechanisms in active ileocolic and colic Crohn's disease.

Copyright © 2003 Marcel Dekker, Inc.

VI. ORAL ROUTE: ROLE OF EXCIPIENTS AND COATINGS

Since it is virtually impossible to treat the ascending colon via the rectum, oral treatment is the only reliable method of delivery. Colonic delivery via the oral route requires control of four factors: time of release, site of release, extent of dispersion, and modification of low flux across the absorptive epithelium. Certain components provide specific mechanisms by which colonic targeting may be achieved. Generally they can be grouped as follows.

A. Specific

By definition, these must take account of the only nonmammalian cue: the colonic bacteria. The mechanisms are as follows:

1. pH-sensitive polymers, which will dissolve at the low pH associated with the cecal metabolism of polysaccharide (soluble fiber)
2. Azoreduction of polymers containing bonds that can be cleaved by reductive scission
3. Fermentable biopolymers in which the glycosidic bonds are broken by simple cleavage or more complete breakdown to short-chain fatty acids

B. Nonspecific

The other group of trigger mechanisms are fairly nonspecific, at least in terms of relying on the bacteria triggers, and may avoid premature release in the upper gastrointestinal tract by:

1. A combination of enteric coating and conventional time-dependent barrier coat dissolution
2. Swelling systems that may eject (e.g., Pulsincap technology) or burst
3. Eroding systems (e.g., Egalet technology)
4. Those using slowed transit in the colon (pellet dosage forms) to release the majority of the drug when trapped in the ascending colon

VII. CONCLUDING REMARKS

The examples in the chapters that follow show how colonic drug delivery technologies achieve a measure of targeted delivery in the terminal small bowel and through the proximal large bowel. Some of the chapters in this part of the book describe colonic drug delivery technologies that have been, or are being, commercialized. Other chapters describe some of the approaches that are available using a specific approach, such as biopolymers or enteric coatings. Such chapters contain extensive lists of the excipients that are available to achieve colonic drug delivery.

Copyright © 2003 Marcel Dekker, Inc.

In addition, the utilization of an interesting technology that specifically delivers drug for investigational purposes is described. The latter is included here because such inventions help the formulator to determine whether colonic drug absorption is likely to be achievable. This capability makes it a useful tool in the development of a colonic drug delivery technology.

REFERENCES

1. JM Hebden, PJ Gilchrist, RC Spiller, P Boulby, P Gowland, AC Perkins, CG Wilson. Dispersion, transit, water content and ascending colon volumes in subjects treated with lactulose and codeine: scintigraphic and M.R.I assessment. Neurogastroenterol Motil 175:8, 1996.
2. JM Hebden, E Blackshaw, AC Perkins, CG Wilson, RC Spiller. Limited exposure of the healthy distal colon to orally dosed formulation is further exaggerated in active left-sided ulcerative colitis. Aliment Pharmacol Ther 14:155–161, 2000.
3. CG Wilson, M Bakhshaee, HE Stevens, AC Perkins, M Frier, PE Blackshaw, JS Binns. Evaluation of a gastro-resistant pulsed release delivery system (Pulsincap) in humans. J Drug Del 4:201–206, 1997.
4. L Barrow, RC Spiller, CG Wilson. Pathological influences on colonic motility: implications for drug delivery. Adv Drug Del Rev 7:201–218, 1991.
5. O Carrette, C Favier, C Mizon, C Neut, A Cortot, JF Colombel, J Mizon. Bacterial enzymes used for colon-specific drug delivery are decreased in active Crohn's disease. Dig Dis Sci 40:2641–2646, 1995.
6. N Washington, C Washington, CG Wilson. Colon and rectal delivery. In: N Washington, C Washington, CG Wilson, eds. Physiological Pharmaceutics: Barriers to Drug Absorption. London: Taylor & Francis: 2001, pp. 143–180.

Copyright © 2003 Marcel Dekker, Inc.

18
Enteric Coating for Colonic Delivery

Gour Mukherji
Ranbaxy Laboratories Ltd., Gurgaon, India

Clive G. Wilson
Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland

I. INTRODUCTION

The most extensive application of a formulation strategy for colonic delivery has been the employment of enteric coatings on solid substrates. This is a natural development of conventional coating technologies to avoid gastric release thus preventing problems such as degradation, or pharmacological effects including gastric irritation and nausea. The underlying principle of this approach has been employment of polymers that are able to withstand the lower pH values of the stomach, but that disintegrate and release the drug as the pH in the small bowel increases. The principal difference is in the functional use of enteric polymers for delayed release compared to their application for colonic drug delivery. For delayed release, the disintegration and drug release from enteric-coated products should be targeted to the proximal small bowel, while for colonic delivery, release from the enteric-coated system should take place closer to the ileocecal junction. Since gastric acid exposure may affect the subsequent behavior of the polymer further down the tract and gastric emptying is a variable dependent on feeding, idiosyncratic, and temporal differences; this is a fairly challenging task.

Early attempts at targeted delivery to the colon utilized those polymers that had previously been used for enteric coating. These dissolve at pH greater than 7 and longer release times have been achieved by applying the material at a greater coat thickness. The solid substrate is varied and includes tablets, capsules, beads, or microparticles. Subsequent advances in targeted colon delivery have prompted technologists to move to other approaches: for example, a hybrid strat-

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Different Strategies Adopted in the Marketed 5-ASA Products for Colon Delivery

Trade name	Molecule	Formulation strategy
Pentasa®	Mesalazine, 250-mg tablets	Ethyl cellulose–coated pellets to provide lag time for drug release in small intestine
Asacol®	Mesalazine, 400-mg tablets	Tablets coated with methacrylic acid copolymer (Eudragit-S) to cause drug release at pH 7
Salofalc®	Mesalazine, 250-mg tablets	Tablets coated with Eudragit-L
Salazopyrin	Sulfasalazine, 500-mg tablets	5-ASA linked to sulfapyridine through azobonds that are cleaved in colonic microflora
Dipentum®	Olsalazine sodium, 250-mg capsules and 500-mg tablets	5-ASA dimer linked through azobonds and cleaved in colonic microflora

egy employing enteric coating with other excipients or prodrug/coating release approaches based on azoreductase or glycosidic activity of cecal bacteria. As an illustration of formulation approaches to a particular product, Table 1 gives a brief description of some commercial 5-amino salicylate (5-ASA) products utilizing the excipients that are currently available.

II. ENTERIC POLYMER MATERIALS

These materials are applied either dissolved in an organic solvent or as an aqueous dispersion. Traditionally, it has been the practice to restrict enteric polymers dissolving at pH 7 and above for colon targeting. Those dissolving at a pH lower than 7 were used for conventional enteric coating to bypass the stomach. However, the pH in the small intestine probably remains acidic and a discriminating target to facilitate release in colon is hard to spot. From studies with pH telemetry capsules [1], it has been shown that the pH in the small intestine increases from the duodenum (pH 5.4–6.1) to the ileum (pH 7–8). The colon has a slightly lower pH than the small intestine (pH 5.5–7), since the acidity of the colon is determined by the availability of fermentable fiber and presence of bacteria [2]. Racial differences in the pH and transit times in the colon, probably due to diet, have also been observed.

Selection of enteric polymer dissolving at pH $\geq$ 7 is likely to cause drug release in terminal small bowel. Optimization of coat thickness is essential to ensure drug release occurs in the colon and does not traverse the entire gastroin-

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Phthalate-Based Enteric Polymers

Polymer	Threshold pH	Brand names	Manufacturer
Cellulose acetate phthalate	6.0–6.4	C-A-P Aquacoat CPD	Eastman FMC
Hydroxypropyl methylcellulose phthalate 50	4.8	H.P.M.C.P. 50 HP-50	Eastman Shin-Etsu
Hydroxypropyl methylcellulose phthalate 55	5.2	H.P.M.C.P. 55 HP-55	Eastman Shin-Etsu
Polyvinylacetate phthalate	5.0	Sureteric	Colorcon

testinal tract. The list of enteric polymeric materials commercially available is given in Tables 2–4. Adjustments to the thickness of enteric polymer coat will help to extend the choice to those dissolving at pH less than 7. Employment of imaging techniques, especially scintigraphy of the formulation in the gastrointestinal tract, has been found to be a useful tool in optimizing coat thickness.

A. Cellulose Acetate Phthalate (CAP)

A number of phthalate-based enteric polymers have been exploited commercially (Table 2). CAP is a white free-flowing powder with a slight odor of acetic acid (Fig. 1). It is insoluble in water, alcohols, and chlorinated hydrocarbons, but soluble in acetone and its mixtures with alcohols, ethyl acetate–IPA mixture, and aqueous alkali (pH 6). The pseudolatex version (Aquacoat CPD) offers the convenience of aqueous-based processing.

Table 3 Methacrylic Acid–Based Copolymers

Polymer	Threshold pH	Brand names	Manufacturer
Methacrylic acid–methyl methacrylate copolymer (1:1)	6.0	Eudragit L 100/L 12.5	Rohm GmbH
Methacrylic acid–methyl methacrylate copolymer (2:1)	6.5–7.5	Eudragit S 100/S 12.5	Rohm GmbH
Methacrylic acid–ethyl acrylate copolymer (2:1)	5.5	Eudragit L 100-55/L 30 D-55 Acryl-EZE Eastacryl 30D	Rohm GmbH Colorcon Eastman

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Miscellaneous Enteric Polymers

Polymer	Threshold pH	Brand names	Manufacturer
Shellac	7.0	—	Zinsser Pangaea Sciences
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	7.0	Aqoat AS-HF	Shinetsu
Poly (methyl vinyl ether/maleic acid) monoethyl ester	4.5–5.0	Gantrez ES-225	ISP
Poly (methyl vinyl ether/maleic acid)*n*-butyl ester	5.4	Gantrez ES-425	ISP

B. Hydroxypropyl Methylcellulose Phthalate (HPMCP)

HPMCP is a white powder or granular material and has been reviewed in many publications. It is a more flexible polymer than CAP. Commercially, the available forms are HPMCP-50 and HPMCP-55. The numbers refer to pH ($\times 10$) of the aqueous buffer solubility. HPMCP is insoluble in water but soluble in alkaline media (pH 4.5) and in an acetone-water mixture.

C. Polyvinylacetate Phthalate (PVAP)

PVAP is soluble in methanol and its mixtures with methylene chloride, ethanol and ethanol-water, and acetone, and its mixtures with alcohols, ethyl acetate–

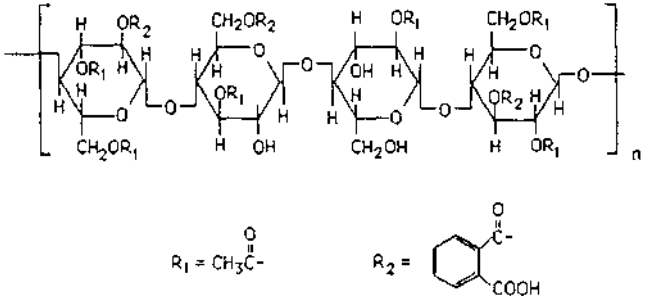


Figure 1 Cellulose acetate phthalate (CAP).

Copyright © 2003 Marcel Dekker, Inc.

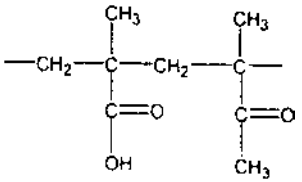


Figure 2 Eudragit L100/S100.

isopropyl alcohol mixture, and alkali (pH 5). Sureteric® is an aqueous dispersion of PVAP.

D. Methacrylic Acid Copolymers

These are anionic copolymers and are very commonly utilized for enteric coating, including application in colonic delivery. This range of copolymers is principally marketed by Röhm Pharma (Darmstadt, Germany) under the brand name Eudragit®. The enteric grades of Eudragit dissolve at raised pH owing to ionization of the carboxyl groups forming salts. The most commonly employed methycrylate polymers are Eudragit L and Eudragit S (Fig. 2), which are copolymers of methacrylic acid and methyl methacrylate and are available as fine solids. Their aqueous solubility depends on the ratio of carboxyl to ester groups, being approximately 1:1 in Eudragit L 100 and 1:2 in Eudragit S 100. This has a direct effect on solubility with regard to pH sensitivity, and these copolymers dissolve at pH 6 and pH 7, respectively.

Eudragit L 100-55 (Fig. 3) is a copolymer of methacrylic acid and ethyl acrylate, and it dissolves at pH above 5.5. Among the anionic copolymers, it is the only polymer that is available as an aqueous, ready-to-use 30% dispersion (Eudragit L30D-55). Others are recommended for use with dissolution media such as acetone or alcohols.

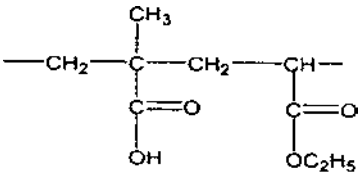


Figure 3 Eudragit L 100-55.

Copyright © 2003 Marcel Dekker, Inc.

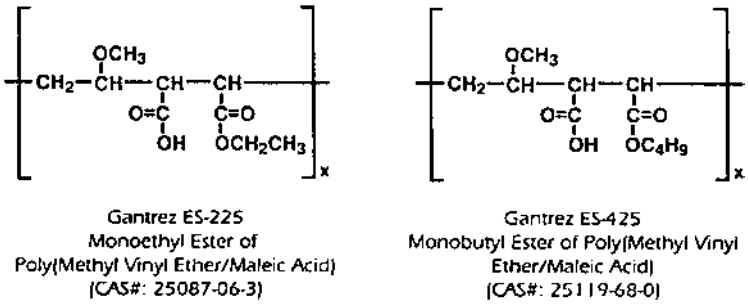


Figure 4 Gantrez ES-225 and Gantrez ES-425.

Eudragits L 100, S 100, and L 100-55 are listed in USNF as methacrylic acid copolymers A, B, and C, respectively.

E. Shellac

Shellac is a material of natural origin and is now less popular in commercial pharmaceutical applications for enteric coatings. It is a purified resinous secretion of the insect *Laccifer lacca*. It is soluble in aqueous alkali at pH of 7.0 and suited for drug release in distal small intestine.

F. Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)

HPMCAS consists of a cellulose backbone to which are attached methyl, hydroxypropyl succinate, and hydroxymethyl acetate groups. The ratio of these side groups affects the extent to which the polymer becomes soluble in the intestine. It dissolves in aqueous buffers of pH 7.

G. Polymethyl Vinyl Ether/Maleic Acid Copolymers

International Speciality Products (ISP) markets a range of polymethyl vinyl ether copolymers under the brand Gantrez (Fig. 4). The ES series of Gantrez are available in ethyl (ES-225), *n*-propyl, or *n*-butyl ester (ES-425) forms and are supplied as a 50% solution in ethanol. They are insoluble in aqueous acidic pH conditions and are suitable for use as enteric materials.

Copyright © 2003 Marcel Dekker, Inc.

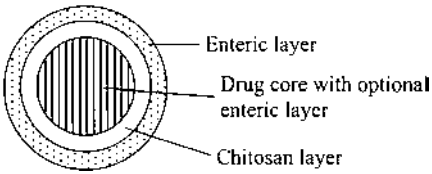


Figure 5 Coated solid dosage form suitable for oral administration described by Sekigawa and Onda [3].

III. EXAMPLES OF ENTERIC-COATED SYSTEMS FOR COLONIC DELIVERY

Sekigawa and Onda claim a coated solid dosage form suitable for oral administration target to the large intestine (Fig. 5) [3]. The product is prepared by coating a core containing the active ingredient, first with a chitosan having a specified degree of deacetylation and a defined degree of polymerization, and then top-coating with any enteric-soluble polymer, such as hydroxypropyl methylcellulose acetate succinate. The targeted release of the active ingredient in the large intestine is reliable when, prior to coating with chitosan, the core is provided with an enteric undercoating layer.

An oral pharmaceutical preparation for releasing a principal agent in the upper gastrointestinal tract was reported by Yamada and co-workers [4], comprising an active component and a solid organic acid, filled into a hard capsule composed mainly of chitosan. The surface of the filled capsule was coated with an enteric coating film consisting of hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate phthalate, methacrylate copolymer, and shellac.

A controlled-release coated bead formulation [5] has been designed such that there is a lag phase prior to the release of the drug that is so measured that the upper colon area can be safely reached and the active substance be supplied there at a predetermined rate to the colon (Fig. 6). It consists of drug layering on an inert seed followed by a drug release control membrane, which is either a pH-independent or pH-dependent first membrane (typically, an enteric polymer). The next layer is an acid layer, followed by a time-controlling compound membrane consisting of a pH-sensitive polymer as an inner layer and an insoluble polymer in the outer layer.

The use of Eudragit S was first described by Dew and colleagues for the targeted delivery of 5-ASA in colitic patients [6] and more recently Adkin and colleagues carried out scintigraphic studies in volunteers to ascertain the behavior

Copyright © 2003 Marcel Dekker, Inc.

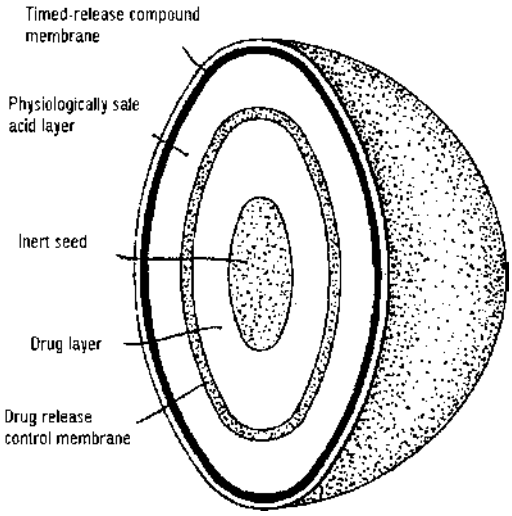


Figure 6 Controlled-release bead formulation designed such that there is a lag phase prior to the release of the drug that is so measured that the upper colon area can be safely reached and the active substance supplied there at a predetermined rate to the colon [5].

of formulations for colonic drug delivery systems containing biodegradable polymers in the matrix and coated with Eudragit L [7].

Ishibashi's group prepared four kinds of capsules for colon delivery containing theophylline, each of which had a different in vitro dissolution lag time [8]. The capsules also contained sulfasalazine as a marker to indicate arrival at the colon. A powdered mixture consisting of 20 mg of theophylline, 50 mg of sulfasalazine, and 100 mg of succinic acid was filled into a hard gelatin capsule, and the joint of the capsule body and cap was sealed with a small amount of 5% (w/w) ethylcellulose ethanolic solution. Four batches of the sealed capsules were spray-coated with ethanolic solutions containing different amounts of Eudragit E (0, 11, 21, and 33 mg/capsule) to provide a different onset time for drug release. Each batch of the Eudragit-E-coated capsules were then coated with a hydrophilic intermediate layer containing hydroxypropyl methylcellulose and acetaminophen, in a hydroxyethanolic solution. Finally, the capsules were coated with hydroxypropyl methylcellulose acetate succinate as the outmost enteric layer. Succinic acid was used as the pH-adjusting agent.

Marvola and co-workers at the University of Helsinki described the use of a multiple-unit system for drug release in the colon using enteric polymers [9]. Film-coated matrix pellets were prepared with enteric polymers as both binders

Copyright © 2003 Marcel Dekker, Inc.

and coating materials. It was found that drug release from the formulations took place in the distal part of the small intestine and the colon if enteric polymers dissolving at pH 7 were employed.

Fukui and colleagues described the use of enteric-coated, timed-release, press-coated tablets [10]. The tablet core contained diltiazem hydrochloride as a model drug, which was enclosed by an outer press-coated shell of hydroxypropylcellulose and, finally, an outermost shell of an enteric polymer. The tablets were found potentially useful for oral site-specific drug delivery including colon targeting.

Gupta et al. utilized a pellet-based colon delivery system for 5-aminosalicylic acid [11]. The core was prepared by drug layering on nonpareil beads followed by coating with an inner layer of a combination of two pH-independent ammonio-methacrylate copolymers (Eudragit RL and RS), and an outer layer of a pH-dependent methacrylic acid copolymer, Eudragit FS.

Krogars et al. prepared pH-sensitive matrix pellets for colon-specific drug delivery of ibuprofen [12]. Using an extrusion-spheronization pelletization technique, Eudragit S and citric acid were the principal formulation variables in the matrix core, which also had microcrystalline cellulose. The pellets were enteric-coated to achieve a lag of 15 min in pH 7.4 phosphate buffer.

IV. CONCLUDING REMARKS

Indirectly, the use of a pH-based trigger to target the colon utilizes bacterial metabolism, which by fermentation of soluble fibers lowers the local pH to around 5; however, it is necessary to avoid premature release in the upper gastrointestinal tract by providing a barrier coat that does not start to dissolve until the unit empties from the stomach. Thereafter a time-dependent system has to be employed since conditions remain fairly homogeneous within the gut lumen until the ileocecal junction is reached.

The physical form of the formulation will strongly influence the retention in the ascending colon since particulates are retained to a greater extent compared to monoliths. Thus the variables of transit and pH combine to make enteric systems somewhat unreliable.

REFERENCES

1. JG Hardy, DF Evans, I Zaki, AG Clark, HH Tonnenson, ON Gamst. Evaluation of an enteric-coated tablet using gamma scintigraphy and pH monitoring. Int J Pharm 37:245–250, 1987.

Copyright © 2003 Marcel Dekker, Inc.

2. SM Reddy, VR Sinha, DS Reddy. Novel oral colon-specific drug delivery systems for pharmacotherapy of peptide and nonpeptide drugs. Drugs Today 35:537–580, 1999.
3. F Sekigawa, Y Onda. Coated solid medicament form having releasability in large intestine. US patent 5,217,720, 1993.
4. A Yamada, T Wato, N Uchida, M Fujisawa, S Takama, Y Inamoto. Oral pharmaceutical preparation released in the gastrointestinal tract. US patent 5,468,503, 1995.
5. K Klokkers-Bethke, W Fischer. Pharmaceutical preparation to be administered orally with controlled release of active substance and method for manufacture. US patent 5,472,710, 1995.
6. MJ Dew, REJ Ryder, N Evans, N Evans, J Rhodes. Colonic release of 5-aminosalicylic acid from an oral preparation in active ulcerative colitis. Br J Clin Pharmacol 16:185–187, 1983.
7. DA Adkin, CJ Kenyon, EI Lerner, I Landau, E Strauss, D Caron, A Penhasi, A Rubinstein, IR Wilding. The use of scintigraphy to provide "proof of concept" for novel polysaccharide preparations designed for colonic drug delivery. Pharm Res 14:103–107, 1997.
8. T Ishibashi, K Ikegami, H Kubo, M Kobayashi, M Mizobe, H Yoshina. Evaluation of colonic absorbability of drugs in dogs using a novel colon-targeted delivery capsule (CTDC). J Control Rel 59:361–376, 1999.
9. M Marvola, P Nykänen, S Rautio, N Isonen, AM Autere. Enteric polymers as binders and coating materials in multiple-unit site-specific drug delivery systems. Eur J Pharm Sci 7:259–267, 1999.
10. E Fukui, N Miyamura, K Uemura, M Kobayashi. Preparation of enteric-coated timed-release press-coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. Int J Pharm 204:7–15, 2000.
11. VK Gupta, TE Beckert, JC Price. A novel pH- and time-based multi-unit potential colonic drug delivery system. I. Development. Int J Pharm 213:83–91, 2001.
12. K Krogars, J Heinamaki, J Vesalahti, M Marvola, O Antikainen, J Yliruusi. Extrusion-spheronization of pH-sensitive polymeric matrix pellets for possible colonic drug delivery. Int J Pharm 199:187–194, 2000.

Copyright © 2003 Marcel Dekker, Inc.

19
Biopolymers and Colonic Delivery

Gour Mukherji
Ranbaxy Laboratories Ltd., Gurgaon, India

Clive G. Wilson
Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland

I. INTRODUCTION

Conventional controlled-release products for oral administration normally lack any property that would facilitate drug targeting to a specific location in the gastrointestinal tract. In spite of this, any slow-release system having a drug-release-time profile extending beyond 6–8 h is likely to be present in the colon for release of a high proportion of the drug payload. If the formulation has the appropriate dissolution control, the drug is able to permeate the colonic epithelium, and if the half-life is sufficient to achieve therapeutic concentrations, the pharmacokinetic profile can be maintained for longer. This forms the basis of once-a-day or twice-a-day therapy, which is expected to increase efficacy by helping compliance.

Biopolymers, particularly those that have pronounced swelling properties, have been frequently employed in the formulation of controlled drug release products. Since many of these polymers may release some of the drug in the upper gastrointestinal tract, the product may be enteric-coated to ensure minimal drug release in the stomach and proximal small intestine. Time-delayed coated systems with appropriate lag time produced by sufficient thickness of barrier coat may serve a similar purpose.

The mode of drug release from colon-targeted biopolymer systems can include one or more of the following mechanisms:

1. Diffusion
2. Polymer erosion
3. Microbial degradation
4. Enzymatic degradation (mammalian and/or bacterial)

Copyright © 2003 Marcel Dekker, Inc.

In addition, drug solubility and formulation of polymer mixes play important roles in determining the extent of drug delivery and release in the colon.

Two broad categories of biopolymers have been employed for formulating colonic systems: (1) biodegradable and (2) nonbiodegradable polymers.

II. BIODEGRADABLE SWELLING POLYMERS

The biodegradable swelling polymers are normally of natural origin and are degraded by the colonic microflora. These materials are fermentable polysaccharides. The colonic microflora secretes a number of enzymes that are capable of hydrolytic cleavage of glycosidic bonds. These include β-D-glucosidase, β-D-galactosidase, amylase, pectinase, xylanase, α-D-xylosidase, and dextranases.

The biodegradable polymers are hydrophilic in nature and may have limited swelling characteristics in acidic pH. However, these polymers swell in the more neutral pH of the colon. Although the rate of drug release is governed to a limited extent by physical factors such as diffusion and drug solubility, the major mechanism of drug release is by matrix erosion produced by enzymatic or microbial interaction with the polymers.

The biodegradable polysaccharides can be employed (a) in the formulation matrix, or (b) as a coat, alone or in combination. Many of these polysaccharides have limited release control properties owing to high water solubility. Hence, they are employed in formulations in the following ways: (a) combination with synthetic nonbiodegradable polymers, or (b) synthetic modification such that solubility is decreased without compromising on their specific degradation in the human colon. The modification is normally done by introduction of groups by: (a) covalent linkages or (b) reversible complexation processes.

A. Guar Gum

Guar gum is a galactomannan polysaccharide (β-1,4 D-mannose, α-1,6 D-galactose) having (1→4) linkages. It has a side-branching unit of monomeric D-galactopyranose joined at alternate mannose unit by (1→6) linkage. It has low water solubility but hydrates and swells in cold water forming viscous colloidal dispersions or sols. The viscosity of a guar gum solution incubated with a homogenate of feces will be reduced by 75% over 40 min [1]. It is susceptible to galactomannase enzyme in the large intestine.

Wong and colleagues [2] reported the evaluation of the dissolution of dexamethasone and budesonide from guar-gum-based matrix tablets using USP Apparatus III. The presence of low-grade HPMC (Methocel E3) or higher-grade HPMC (Methocel E50 LV) in dexamethasone formulations altered the rate of the matrix degradation.

Copyright © 2003 Marcel Dekker, Inc.

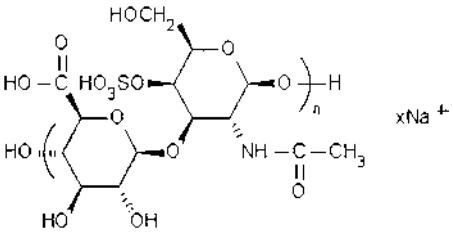


Figure 1 Chondroitin sulfate.

Krishnaiah et al. [3] described a scintigraphic study using technetium-99m-DTPA as a tracer, incorporated into tablets to follow the transit and dissolution. Scintiscans revealed that some tracer was released in stomach and small intestine but the bulk of the tracer present in the tablet mass was delivered to the colon.

Rubinstein and Gliko-Kabir [4] reported cross-linking of guar gum with borax to enhance its drug-retaining capacity.

B. Chondroitin Sulfate

Chondroitin sulfate is a soluble mucopolysaccharide consisting of β-1,3 D-glucuronic acid linked to *N*-acetyl-D-galactosamide (Fig. 1). It is a substrate for the *Bacteroides* sp. in the large intestine. Natural chondroitin sulfate is readily water soluble and may not be able to sustain the release of many drugs from the matrix. Rubinstein and co-workers [5] have reported the use of cross-linked chondroitin sulfate (Fig. 2) as a carrier for indomethacin specifically for the large bowel. Since natural chondroitin sulfate is readily water soluble, it was cross-linked with 1,12-diaminododecane. The cross-linked polymer was blended with indomethacin and compressed into tablets. There was enhanced release on incubation with rat cecal contents.

C. Pectin

Pectin is a heterogeneous polysaccharide composed mainly of galacturonic acid and its methyl ester. It consists of a backbone of α-1,4 D-galacturonic acid and

ChS-CONH-$(CH_2)_{12}$-NHCO-ChS

(where ChS = chrondrotin sulphate)

Figure 2 Dimer of chondroitin sulfate.

Copyright © 2003 Marcel Dekker, Inc.

1,2 L-rhamnose with D-galactose and L-arabinose side chains. It remains intact in stomach and small intestine but is degraded by colonic bacterial enzymes. Pectins with high degrees of methoxylation can be employed for colonic drug delivery. Alternatively, pectins with low degrees of methoxylation can be cross-linked with a carefully controlled amount of a divalent cation, typically calcium [6]. Sriamornsak and colleagues [7] coated theophylline pellets with calcium pectinate and reported a pH-dependent in vitro release in 4 h. Wakerly and colleagues coated paracetamol tablets using a combination of pectin and ethylcellulose, in the form of an aqueous dispersion [8]. Based upon in vitro dissolution, it was concluded that such a system can be used for targeted colonic drug delivery.

Pectins with low degree of methoxylation can also undergo amidation of carboxylic acid groups. Munjeri and colleagues reported entrapment of indomethacin and sulfamethoxazole inside amidated pectin, gelled in the presence of calcium [9]. The drug-containing core was coated by a chitosan polyelectrolyte complex to obtain the desired release pattern in simulated intestinal media.

Adkin and colleagues at Nottingham carried out scintigraphic studies to ascertain the behavior of formulations for colonic drug delivery systems containing biodegradable polymers in the matrix and coated with Eudragit L [10]. Two calcium pectinate (CaP) matrix formulations were developed as potential colon-targeting systems. One formulation contained calcium pectinate and pectin (CaP/P) and was designed to rapidly disintegrate in the ascending colon. The second formulation contained calcium pectinate and guar gum (CaP/GG) and was designed to disintegrate more slowly than (CaP/P), releasing its contents throughout the ascending and transverse colon. Both formulations were enteric-coated by spray coating with aqueous dispersion of Eudragit L. Scintigraphic evaluation was carried out in 10 healthy volunteers and fermentation of the polymer confirmed in rats. Complete tablet disintegration for formulation CaP/GG appeared to be slower than that of CaP/P and the time and the location of complete tablet disintegration was more reproducible with CaP/P compared to CaP/GG.

D. Amylose

Amylose is a linear polymer of glucopyranose units (α-1,4 D-glucose) linked through α-D-(1,4)-linkages (Fig. 3). The molecule usually consists of around 1000–5000 glucose units. Amylose is resistant to pancreatic amylases but is susceptible to those of bacterial origin. Alone, the biopolymer becomes porous on hydration. Addition of ethyl cellulose produces a polymer mixture suitable for colon targeting [11].

Ring and co-workers claimed delayed-release compositions comprising an active compound and amorphous amylose and having an outer coating comprising a film-forming cellulose or acrylic polymer material [12]. The amorphous amylose is glassy amylose and is of particular value for selective release into the

Copyright © 2003 Marcel Dekker, Inc.

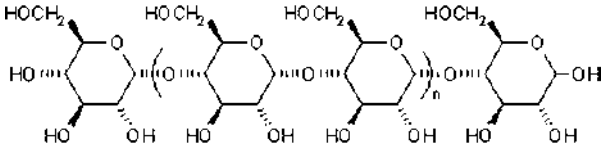


Figure 3 Amylose.

colon. As compared to the other form of amylose, which is a rubbery compound, amorphous amylose exists in a glassy state below the glass transition temperature. Film-forming cellulosics are usually based on ethyl cellulose.

In another application, Cartilier and colleagues prepared sustained-release tablets containing drug and non-cross-linked substituted amylose [13]. Substituted amylose is prepared by reacting the hydroxy groups in amylose with a reactive function such as an epoxy group. Usual organic substituents include epoxy, halide, and isocyanate-containing groups.

E. Dextran

Dextran is a polysaccharide consisting of α-1,6 D-glucose and α-1,3 D-glucose units. Dextran hydrogels are stable when incubated at 37°C with the small-intestinal enzymes amyloglucosidase, invertase, and pancreatin [14]. However, they are degraded by dextranases, which is a microbial enzyme found in the colon. Hovgaard and Brondsted prepared dextran hydrogels by cross-linking with diisocyanate [15]. These hydrogels were characterized by equilibrium degree of swelling and mechanical strength. Release of entrapped hydrocortisone was found to depend on the presence of dextranases in the release medium.

F. Starch

Starch (Fig. 4) is composed of (a) amylose and (b) amylopectin. The latter is a branched polysaccharide composed of around 10,000 glucose units. Starch is

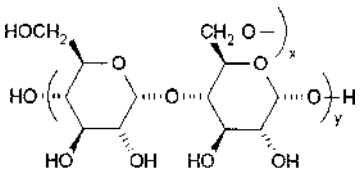


Figure 4 Starch.

Copyright © 2003 Marcel Dekker, Inc.

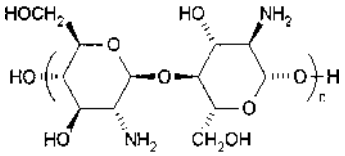


Figure 5 Chitosan.

hydrolyzed by several amylolytic enzymes in the gut. The degradation products are mainly composed of oligosaccharides, dextrins, and maltose. A colonic drug delivery composition has been described using starch capsules to contain the drug followed with a coating [16]. The coating may be a pH-sensitive material, a redox-sensitive material, or a material broken down by specific enzymes or bacteria present in the colon.

G. Chitosan

Chitosan is a poly (2-amino 2-deoxy D-glucopyranose) in which the repeating units are linked by (1–4) β-bonds (Fig. 5). It is biodegradable and nontoxic. It dissolves in the acidic pH of the stomach but swells at pH 6.8. Tominaga and colleagues prepared a composite for delivery to the colon comprising an active core, an internal layer comprising chitosan, and an external layer, coated on the internal coating layer, containing zein [17]. Zein protects the contents by being acid resistant but undergoing proteolysis in the small intestine. Chitosan in the internal layer prevents the elution of the active ingredients in the core in the small intestine. However, in the large intestine the chitosan film breaks owing to the combined effect of microorganisms and osmotic pressure.

H. Cyclodextrin

Cyclodextrin is a cyclic oligosaccharide consisting of at least six glucopyranose units joined by α-(1 → 4) linkages (Fig. 6). It is produced by a highly selective

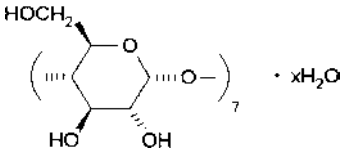


Figure 6 Cyclodextrin.

Copyright © 2003 Marcel Dekker, Inc.

enzymatic synthesis. The cyclodextrins consist of six, seven, or eight glucose monomers arranged in a doughnut-shaped ring, which are denoted α-, β-, or γ-cyclodextrin, respectively. The specific coupling of the glucose monomers gives the cyclodextrin a rigid, truncated conical molecular structure with a hollow interior of a specific volume. This internal cavity, which is lipophilic, can incorporate hydrophobic materials, and is a key structural feature of cyclodextrin, providing the ability to complex molecules including aromatics, alcohols, halides and hydrogen halides, carboxylic acids, and their esters [18].

Cyclodextrins can be fermented to small saccharides by colonic microflora, whereas they are only slowly hydrolyzable in the conditions of the upper gastrointestinal tract. This characteristic, as with the other fermentable saccharides, may be exploitable for colon-specific delivery.

Uekama and colleagues selectively conjugated an anti-inflammatory drug, 4-biphenylylacetic acid (BPAA) onto one of the primary hydroxyl groups of α-, β-, and γ-cyclodextrins through an ester or amide linkage [19]. BPAA was found to be released after the ring opening followed by ester hydrolysis, and the activation took place site-specifically in the cecum and colon.

Siefke and colleagues reported biodegradable physical mixtures of methacrylic acid copolymers (Eudragit®-RS) and β-cyclodextrins [20].

I. Inulin

Inulin (Fig. 7) is a naturally occurring glucofructan that can resist hydrolysis and digestion in the upper gastrointestinal tract. It is fermented by colonic microflora. Inulin, with a high degree of polymerization, was formulated as a biodegradable colon-specific coating by suspending it in Eudragit RS films. The films withstood gastric and intestinal fluid but were degraded by fecal media [21].

Vinyl groups were introduced in inulin chains to form hydrogels, by reacting with glycidyl methacrylate [22]. Enzymatic digestibility of the prepared hydrogels was assessed by performing an in vitro study using an inulinase preparation derived from *Aspergillus niger*. Equilibrium swelling ratio and mechanical strength of the hydrogels were also studied. Based upon the mode of swelling it was concluded that inulin-degrading enzymes were able to diffuse into the inulin hydrogel networks causing bulk degradation [23].

III. NONBIODEGRADABLE SWELLING POLYMERS

Nonbiodegradable polymers are more frequently employed in controlled-release systems rather than in targeted colonic delivery. These polymers are frequently synthetic and undergo dissolution or disintegration in the gastrointestinal tract, without undergoing significant absorption or degradation. They are generally

Copyright © 2003 Marcel Dekker, Inc.

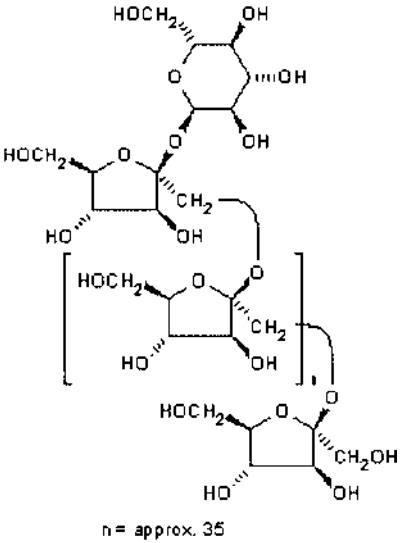


Figure 7 Inulin.

nonspecific carrier systems. Employment of these polymers as carrier matrices for colonic delivery may require a pH- or time-dependent coat for colon specificity. For this reason, products have been commonly formulated containing such polymers in a drug core, followed by application of an enteric polymer coat for preventing drug release in the stomach and the upper intestine.

The solubility characteristics of the active substance can also play an important role. If a drug has high and pH-independent solubility profile, the selection of polymer system for targeted drug delivery, particularly to the colon, is an extremely challenging task. Such matrices tend to release the drug, partially or significantly, in the stomach and the small intestine. Increased proportions of the polymer may cause incomplete drug release in the colon. Drugs having poor solubility may have intrinsic problems in absorption in the water-deficient colon.

Nonbiodegradable swelling polymers do not undergo any cleavage by enzymes or microbes present in the lumen. The prominent examples include the cellulose ethers and the cross-linked polyacrylates. Among the celluloses, there are various grades of hydroxymethyl propylcellulose (HPMC), which are graded based upon viscosity. These excipients are commercially marketed under the trade name Methocel® by Dow. Other cellulose ethers include methyl cellulose, hydroxypropyl cellulose, and carboxymethyl cellulose. The cross-linked polyacrylates of the swelling types include the branded Carbopols of the oral grade, with suffix 934P, 974P, and 971P, manufactured by Noveon (formerly BF Goodrich).

Copyright © 2003 Marcel Dekker, Inc.

Finally, there have been many patents that attempt to exploit azoreductase activity in the colon. Azo-networks based on an acrylic backbone cross-linked with 4,4′-divinylazobenzene were prepared and evaluated for drug delivery and mucoadhesive interactions. The data obtained by Kakoulides and colleagues indicated that there is an optimum cross-linking density to allow nonadhesive particles to reach the colon. Within the colonic environment, the azo-network degrades to produce a structure capable of developing mucoadhesive interactions with the colonic mucosa [24].

IV. CONCLUDING REMARKS

The attempt to utilize trigger mechanisms in the design of colon-targeted drug delivery systems has generally relied on the marked increase in bacterial density to 10^{11}–10^{12} colony-forming units per mL up from 10^5–10^7 as the drug formulation moves from the terminal ileum to caecum. Caecal metabolism is therefore one of the most important triggers to produce colon-targeting in man.

An important issue that should be considered when targeting drugs to the colon is that differences in diet and the prevalent pathological condition may alter the response between individuals. For example, there can be as much as a four to six times increase in methane and hydrogen production after a stimulatory meal in certain individuals. This is certainly an additional variable that reflects the redox potential generated by the microflora and the supply of appropriate nutrients.

REFERENCES

1. A Tomlin, NW Read, CA Edwards, BI Duerden. The degradation of guar gum by a fecal incubation system. Br J Nutr 55:481–486, 1986.
2. D Wong, S Larrabee, K Clifford, J Tremblay, DR Friend. USP dissolution apparatus III (reciprocating cylinder) for screening of guar-based colonic delivery formulations. J Control Rel 47:173–179, 1997.
3. YSR Krishnaiah, S Satyanarayana, YVR Prasad, SN Rao. Gamma scintigraphic studies on guar gum matrix tablets for colonic drug delivery in healthy human volunteers. J Control Rel 55:245–252, 1998.
4. A Rubinstein, I Gliko-Kabir. Synthesis and swelling dependent enzymatic degradation of borax modified guar gum for colonic delivery purposes. STP Pharma Sci 5: 41–46, 1995.
5. A Rubinstein, D Nakar, A Sintov. Colonic drug delivery: enhanced release of indomethacin from cross-linked chondroitin matrix in rat cecal content. Pharm Res 9: 276–278, 1992.
6. M Ashford, J Fell, D Attwood, H Sharma, P Woodhead. Studies on pectin formulations for colonic drug delivery. J Control Rel 30:225–232, 1994.

Copyright © 2003 Marcel Dekker, Inc.

7. P Sriamornsak, S Prakongpan, S Puttipipatkhachorn, RA Kennedy. Development of sustained release theophylline pellets coated with calcium pectinate. J Control Rel 47:221–232, 1997.
8. Z Wakerly, JT Fell, D Attwood, D Parkins. Pectin/ethylcellulose film coating formulations for colonic drug delivery. Pharm Res 13:1210–1212, 1996.
9. O Munjeri, JH Collett, JT Fell. Hydrogel beads based on amidated pectins for colon-specific drug delivery: the role of chitosan in modifying drug release. J Control Rel 46:273–278, 1997.
10. DA Adkin, CJ Kenyon, EI Lerner, I Landau, E Strauss, D Caron, A Penhasi, A Rubinstein, IR Wilding. The use of scintigraphy to provide "proof of concept" for novel polysaccharide preparations designed for colonic drug delivery. Pharm Res 14:103–107, 1997.
11. S Milojevic, JM Newton, JH Cummings, GR Gibson, RL Botham, SG Ring, M Stockham, MC Allwood, Amylose as a coating for drug delivery to the colon: preparation and in vitro evaluation using 5-aminosalicylic acid pellets. J Control Rel 38: 75–84, 1996.
12. SG Ring, DB Archer, MC Allwood, JM Newton. Delayed release formulations. US patent 5,294,448, 1994.
13. L Cartilier, I Moussa, C Chebli, S Buczkowski. Substituted amylose as a matrix for sustained drug release. US patent 5,879,707, 1999.
14. L Simonsen, L Hovgaard, PB Mortensen, H Brondsted. Dextran hydrogels for colon-specific drug delivery. 5. Degradation in human intestinal incubation models. Eur J Pharm Sci 3:329–337, 1995.
15. L Hovgaard, H Brondsted. Dextran hydrogels for colon-specific drug delivery. J Control Rel 36:159–166, 1995.
16. P Watts. Colonic drug delivery composition. US patent 6,228,396, 2001.
17. S Tominaga, T Takizawa, M Yamada. Large intestinal delivery composite. US patent 6,248,362, 2001.
18. WE Wood, NJ Beaverson. Barrier material comprising a thermoplastic and a compatible cyclodextrin derivative. US patent 6,218,013, 2001.
19. K Uekama, K Minami, F Hirayama. 6(A)-O-[(4-biphenylyl)acetyl]-alpha-, beta- and gamma-cyclodextrins and 6(A)-deoxy-6(A)-[[(4-biphenylyl)acetyl]-amino]-alpha-, beta- and gamma-cyclodextrins: potential prodrugs for colon-specific delivery. Med Chem 40:2755–2761, 1997.
20. V Siefke, HP Weckenmann, KH Bauer. β-Cyclodextrin matrix films for colon-specific drug delivery. Proc Int Symp Control Rel Bioact Mater 20:182–183, 1993.
21. L Vervoort, R Kinget. In vitro degradation by colonic bacteria of inulin HP incorporated in Eudragit RS films. Int J Pharm 129:185–190, 1996.
22. L Vervoort, G Vanden Mooter, P Augustins, R Bousson, S Toppet, R Kinget. Inulin hydrogels as carriers for colonic drug targeting. I. Synthesis and characterization of methacrylated inulin and hydrogen formation. Pharm Res 14:1730–1737, 1997.
23. L Vervoort, P Rombaut, G Vanden Mooter, P Augustins, R Kinget. Inulin hydrogels. II. In vitro degradation study. Int J Pharm 172:137–145, 1998.
24. EP Kakoulides, JD Smart, J. Tsibouklis. Azocrosslinked poly(acrylic acid) for colonic delivery and adhesion specificity: in vitro degradation and preliminary ex vivo bioadhesion studies. J Control Rel 54:95–109, 1998.

Copyright © 2003 Marcel Dekker, Inc.

20

Time-Dependent Systems for Colonic Delivery

Wang Wang Lee and Clive G. Wilson
Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland

Gour Mukherji
Ranbaxy Laboratories Ltd., Gurgaon, India

I. INTRODUCTION

Time-dependent systems have been developed for colon-targeted delivery utilizing nonbiodegradable polymers that are more frequently employed as excipients in controlled-release systems. The polymers are usually synthetic in nature and undergo dissolution or disintegration in the gastrointestinal tract, without undergoing significant absorption or degradation. They are generally nonspecific with respect to pH-solubility characteristics and the employment of these polymers as carrier matrices for colonic delivery often utilizes a time-dependent mechanism to provide an initial lag phase of low or no release during transit through the upper gastrointestinal tract. In addition, some of the systems described in the patent literature are based on well-established osmotic core technology. Products have been formulated in a variety of compositions, including incorporation of polymers in a drug core, with an application of an enteric polymer coat for preventing drug release in the stomach. This may provide release in the terminal ileum or, if the lag time is sufficient (3–4 h), in the colon. In another variation, the outermost nonenteric layer completely replaces the enteric inner layer resulting in a complete time-dependent drug release mechanism.

Copyright © 2003 Marcel Dekker, Inc.

II. FORMULATION CONSIDERATIONS

The solubility characteristics of the active substance can play an important role in this type of colonic technology. If a drug has high solubility, the selection of the polymer system for targeted drug delivery, particularly to the colon, is an extremely challenging task. Such matrices may tend to release the drug prematurely, at least partially, in the stomach and the small intestine. Application of a thicker coat of the polymer may cause incomplete drug release in the colon.

In contrast, drugs having poor solubility may have intrinsic problems with regard to absorption from the colon, where the availability of water is less.

Prominent examples of synthetic materials used to develop time-dependent colonic technologies include the cellulosic ethers and the cross-linked polyacrylates. Among the celluloses, there are grades of hydroxypropyl methylcellulose (HPMC) of various viscosities, which are commercially marketed under the trade name Methocel® (Dow). Other cellulose ethers include methyl cellulose, hydroxypropyl cellulose, and carboxymethyl cellulose. The cross-linked polyacrylates of the swelling types include the branded Carbopols of the oral grade, with suffix 934P, 974P, and 971P, manufactured by Noveon (formerly BF Goodrich). Polymethacrylates are often employed in nonswelling polymers in modified-release products. The polymethacrylic acids are frequently employed as enteric polymer coats on matrices, while the anionic, the cationic, and the neutral polymethacrylates have been used in controlled-release products. The most commonly used brands of these polymers are the Eudragits® from Rohm-Haas GmbH. The polyethylene oxides are also useful polymers that are suitable for application in colonic drug delivery.

The following section illustrates some of the technologies that have been commercialized that employ nonbiodegradable polymeric systems for colon-specific delivery.

III. AVAILABLE TECHNOLOGIES

A. Codes

The technology used in the Codes™ system comprises a series of polymers that are combined to protect the drug core until the formulation arrives in the colon. Codes, an oral tablet technology, consists of an enteric outer coating, with a cationic polymer coating for retarding release during transit along the small intestine. Once in the colon, lactulose, which is incorporated in the drug core, is degraded by the colonic microflora allowing drug release.

B. Colon-Targeted Delivery System

This system, first described by Shah and co-workers, uses lag time to achieve colon delivery. The system is comprised of three parts: an outer enteric coat, an

Copyright © 2003 Marcel Dekker, Inc.

inner semipermeable polymer membrane, and a central core comprising swelling excipients and an active component [1]. These parts of the system function to prevent premature release in the upper gastrointestinal tract. The dosage form releases drug consistently in the colon by a time-dependent rupturing mechanism.

The outer enteric coating prevents drug release until the tablet reaches the small intestine. In the small intestine, the enteric coating dissolves allowing gastrointestinal fluids to diffuse through the semipermeable membrane into the core. The core swells until after a period of 4–6 h, when it bursts, and releases the active component in the colon.

The precision and predictability of release time rely on the functional properties of the semipermeable membrane, in particular the percent elongation of the membrane, which increases by between 2.0 and 3.5% during manufacture. This membrane elongation allows the release of the active ingredient 4–6 h after entering the small intestine, which is consistent with the literature values for the small intestine transit time (SITT). The elongation is achieved using a plasticizer that comprises between 10 and 30% w/w of the membrane. The concentration of the plasticizer determines the percentage of elongation.

The enteric coating has a thickness of 100 μm at a weight of about 15% of the core. The polymer used is hydroxypropyl methylcellulose phthalate, which dissolves at pH 5.5. The enteric coating is typically formulated with distilled acetylated monoglyceride as the plasticizer. The role of the membrane is to allow water influx but to prevent outward diffusion of the active drug. Several polymers have suitable properties and include ethylcellulose, cellulose acetate, and polyvinyl chloride. Conventional plasticizers, dibutyl sebacate, acetylated monoglycerides, and diethyl phthalate, are utilized.

In addition to the active component, the core contains a swelling agent, for example, croscarmellose sodium or sodium starch glycolate, and an osmotic agent such as mannitol, sucrose, or glucose in the percentages of 10–30% and 15–25% w/w, respectively.

The formulation is prepared by conventional methods. The core is prepared by wet granulation and the semipermeable and the enteric coating are applied by suitable air spray systems. In vitro dissolution experiments carried out showed that release occurred after 4–6 h exposure of the system to phosphate buffer pH 7.5. This release occurred regardless of the time of initial exposure in an acid medium. These data suggest that this system should be applicable for colonic delivery.

C. Time-Controlled Ethylcellulose System

A novel four-compartment system was described by Niwa and colleagues, which releases drug in a time-controlled system based on an ethylcellulose shell [2]. The base of the system is drilled to permit access of water to a swellable component, which causes rupture of the system at a rate that is dependent upon the

Copyright © 2003 Marcel Dekker, Inc.

thickness of the cap. Published in vivo data from beagle dog studies that investigated cap thicknesses of 39 μm, 63 μm, and 76 μm showed peak plasma peaks of the marker substance fluorescein at 1.5 h, 4 h, and 7 h, respectively, suggesting that the thicker coating may be sufficient to target the colon. Such systems work specifically at low pH and thus administration of this system with food may cause premature release in the upper gastrointestinal tract [3].

D. Oros-CT

The following two examples illustrate the use of osmotic agents to provide colon-targeted delivery. Oros-CT is a technology developed by Alza Corporation and consists of an enteric coating, a semipermeable membrane, a layer to delay drug release, and a core consisting of two compartments. The first compartment contains the active drug in an excipient layer adjacent to an exit passageway and the other is an osmopolymer composition to provide the osmotic push in the system [4].

The enteric coating used does not dissolve, disintegrate, or change its structural nature in the stomach. The material consists of phthalates, keratin, formalin-treated protein, oils, and anionic polymers. The semipermeable wall consists of selectively permeable polymers that are insoluble in body fluids, nonerodible but permeable to the passage of fluids. These polymers (cellulose acylate and cellulose acetates) form good semipermeable membranes.

The layer below the semipermeable membrane consists of polyethers, polyoxyethylene, and hydroxypropylmethylcellulose, depending upon the formulation. It delays the release of drug for about 2–4 h. As the system passes through the small intestine, it absorbs fluid and begins to dispense drug at a controlled rate.

In the core, the osmopolymer swells or expands to push the composition containing the active drug from the delivery system. The osmopolymers are typically hydrophilic polymers including poly(hydroxyalkylmethacrylate), poly(vinylpyrrolidone), and poly(vinylalcohol), or acidic carboxy-polymers.

The compartment containing the active drug and the osmopolymer are manufactured by either wet or dry granulation and the dosage form is formed by tablet press. The wall and the delay coat are formed by an air suspension procedure. The enteric coating is applied onto the surface of the delay layer. On the semipermeable membrane, a 6.35-μm orifice is laser-drilled through to the core components.

The Oros-CT system has been utilized in the delivery of drugs for the treatment of colitis, ulcerative colitis, Crohn's disease, idiopathic prototis, and other conditions affecting the colon [4].

E. Controlled-Release Drug Dellvery Device

The delivery device is an osmotic system with a solid core comprising an active drug, a substantially soluble delay jacket, a semipermeable membrane, and an

Copyright © 2003 Marcel Dekker, Inc.

enteric coating. The delay jacket comprises at least one component selected from the group consisting of a binder, an osmotic agent, and a lubricant. The semipermeable membrane may have a release orifice as a part of the structure [5].

The enteric coating resists dissolution in the gastric fluid and limits drug release in the intestinal fluid. The enteric coating usually consists of phthalate-based material such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, or polyvinyl acetate phthalate. The semipermeable membrane consists of cellulose acetate, ethylcellulose, and polymethacrylic acid esters that function to maintain physical integrity. To impede the dissolution and release of the active agent as the system travels through the small intestine, a jacket delaying release is included in the formulation.

The solid core comprises an active drug and excipients including osmotic agents, lubricants, binders, and suspending agents. The osmotic agent induces a hydrostatic pressure after water enters the core, which drives out the active drug in solution or as a suspension. Suitable osmotic agents include salts of organic or inorganic acids.

The delay jacket may be applied to the core using conventional means, for example a tablet press or a spray coater. This is followed by application of the semipermeable membrane using film-coating techniques and the enteric coating applied utilizing a conventional perforated pan-coating technique.

F. Time Clock

The Time Clock delivery device developed by Pozzi and colleagues is a pulsed delivery system based on a coated solid dosage form. The coating, which is applied by aqueous dispersion, is a hydrophobic-surfactant layer with the addition of a water-soluble polymer to improve adhesion of the coating to the core. The dispersion rehydrates and redisperses once in an aqueous environment in a time proportional to the thickness of the film. Following redispersion, the core is available for dissolution [6].

In vitro studies described by the authors showed that the lag time interval was highly reproducible despite variation of the parameters simulating differing physiological conditions. The authors used the dye sunset yellow E110 to visualize the behavior of the system in vitro. The dissolution of the dye was always rapid and complete for all the tablets tested. In vivo studies confirmed the high reproducibility of the lag time. In a clinical study conducted using scintigraphy, the effect of food was investigated. After the administration of Time Clock following either a low- or a high-calorie meal, the mean lag time for drug release was 345 min and 333 min, respectively.

The hydrophobic film redispersion appears not to be influenced by the presence of intestinal digestive enzymes or by the mechanical action of the stomach. The lag time interval can therefore be considered independent of the digestive state. However, the Time Clock releases its core content at a set lag time, regard-

Copyright © 2003 Marcel Dekker, Inc.

less of the position of the delivery system in the gastrointestinal tract [6]. This is a disadvantage if a positioned site-specific drug delivery is required. Product development work, described by Steed and colleagues in 1997, used a hydrophobic enteric coating to increase the specificity of drug release [7].

IV. SUMMARY

From these descriptions, it is noted that the general construction used for the time-dependent systems is similar. The composition comprises three main components (in the form of layers): an outer enteric coating, a lag phase layer, and a core containing the active component. The characteristics of polymers used to form the layers should be selected to allow sufficient flexibility to provide gastric protection and low release during intestinal transit thereby facilitating delivery to the colon.

REFERENCES

1. NH Shah, AM Railkar, W Phuapradit. Colon targeted delivery system. US patent 6,039,975, 2000.
2. K Niwa, T Takaya, T Morimoto, K Takada. Preparation and evaluation of a time-controlled release capsule made of ethylcellulose for colon delivery of drugs. J. Drug Target 3:83–89, 1995.
3. KI Matsuda, T Takaya, F Shimoji, M Muraoka, M Yoshikawa, K Takada. Effect of food intake on the delivery of fluorescein as a model drug in colon delivery capsule after oral to beagle dogs. J Drug Target 4:59–67, 1996.
4. F Theeuwes, GV Guittard, PSL Wong. Delivery of drug to colon by oral dosage form. US patent 4,904,474, 1990.
5. L Savastano, J Carr, E Quadros, S Shah, SC Khanna. Controlled release drug delivery device. US patent 5,681,584, 1997.
6. F Pozzi, P Furlani, A Gazzaniga, SS Davis, IR Wilding. The Time Clock system: a new oral dosage form for fast and complete release of drug after a predetermined lag time. J Control Rel 31:99–108, 1994.
7. KP Steed, G Hooper, N Monti, MS Benedetti, G Fornasini, IR Wilding. The use of pharmacoscintigraphy to focus the development strategy for a novel 5-ASA colon targeting system ["Time Clock (R)" system]. J Control Rel 49:115–122, 1997.

Copyright © 2003 Marcel Dekker, Inc.

21

New Approaches for Optimizing Oral Drug Delivery: Zero-Order Sustained Release to Pulsatile Immediate Relehase Using the Port System

John R. Crison and Michael L. Vieira
Port Systems LLC, Ann Arbor, Michigan, U.S.A.

Gordon L. Amidon
The University of Michigan, Ann Arbor, Michigan, U.S.A.

I. INTRODUCTION

The Port System is a compartmentalized dosage form that independently controls drug release time and drug release rate for multiple drugs and doses. Advantages associated with this drug delivery system include designing release profiles to optimize drug pharmacokinetics and/or pharmacodynamics and administering more than one dose or drug in a single unit to improve patient compliance. The release profiles that the Port System is capable of range from a zero-order release rate to a pulse to mimic an immediate-release tablet. The latter is particularly useful when the goal is to release drug in the lower ileum or colon. Additional technologies, such as dissolution rate or permeability enhancers, can be combined with the drug to enhance bioavailability.

Copyright © 2003 Marcel Dekker, Inc.

II. HISTORICAL DEVELOPMENT

The Port Systems technology was conceived in the late 1980s to fulfill the industry's need for a versatile delivery system where the release rate and the time of release could be independently controlled [1]. The first patent was issued in the United States on February 7, 1995 [2] and subsequent patents were filed and issued resulting in claims covering the materials, the design, and the manufacture [3–5]. Patents have also been filed in Europe and Japan.

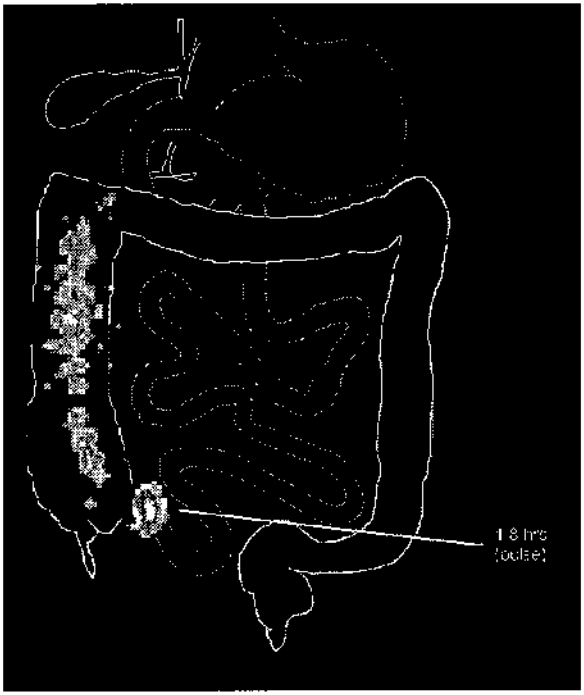
The first human study was conducted in 1995 using hand-compounded dosage forms and consisted of labeling the contents with a gamma emitter and taking scintigraphic images of the in vivo release process (Fig. 1A). The study was conducted in both fed and fasted conditions and the results showed that the time of marker release was not statistically affected by food (Fig. 1B). Since that milestone human scintigraphy study, proof of concept studies evaluating different release strategies using hand-compounded product have been tested in humans and dogs, illustrating not only the versatility of this delivery system but also excellent in vitro–in vivo correlations. In parallel with the aforementioned development activities, the manufacturing process has been made commercially feasible and plans are being made to install the manufacturing equipment at a cGMP facility.

III. DESCRIPTION OF THE TECHNOLOGY

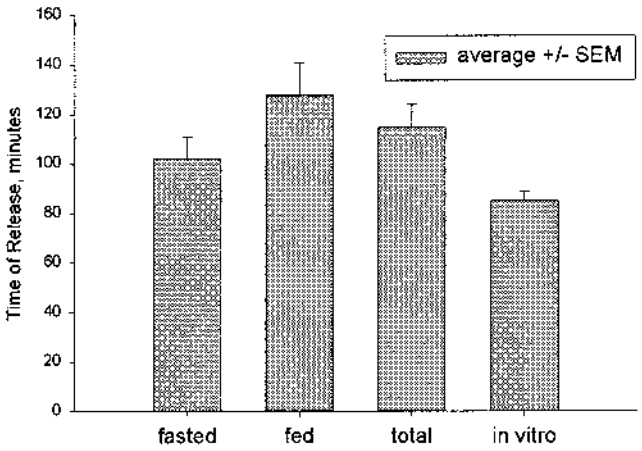
The Port System is based on a semipermeable capsule body divided into compartments by a slidable separator (Fig. 2). The current design is a hydrophilic, swellable container, such as a hard gelatin or hydroxypropyl methylcellulose capsule body that has been coated with a semipermeable film. Inside the capsule body are two compartments formed by a nonswelling, slidable separator. One or both of the compartments can contain drug while the lower compartment below the separator contains water-soluble excipients. The mechanism of action for drug release begins as water diffuses through the semipermeable membrane into the

Figure 1 (A) A scintigraphic image of the Port System releasing samarium chloride in a human subject. The dosage form contained lactose, sorbitol, magnesium stearate, Explotab®, and samarium chloride. After manufacture, radiolabeling was achieved by neutron activation of the intact dosage form, which transformed nonradioactive ^{152}Sm into radioactive gamma-emitting nuclei, ^{153}Sm. The dose was given to six patients under fed and fasted conditions (Scintipharma, Lexington, KY). (B) Summary of scintigraphy study for both fed and fasted subjects. In vitro testing was performed using a USP Apparatus 2, paddle speed 100 rpm, in phosphate buffer, pH 7.5 maintained at 37°C.

Copyright © 2003 Marcel Dekker, Inc.



A



B

Copyright © 2003 Marcel Dekker, Inc.

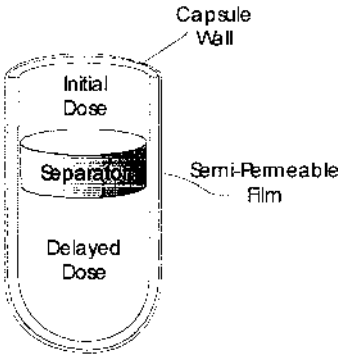


Figure 2 Schematic of the Port System showing two compartments separated with a slidable plug.

capsule body. The water-soluble formulation components contained in the capsule body are solubilized by the influx of water creating an osmotic pressure gradient between the inside of the capsule and the outside gastrointestinal environment. The hydrostatic pressure inside the capsule body pushes the slidable separator out as more water enters the capsule through the membrane. At a predesigned time, the separator slides completely out of the capsule body and the contents are released.

Port System's versatility in independently controlling the rate and the time of drug release makes it possible to tailor a drug release profile to meet the ideal pharmacokinetic and/or pharmacodynamic requirements. The technology can be configured for a variety of drug release profiles by combining immediate with sustained- and/or delayed-release components in the two compartments of the capsule body. Combinations that have been achieved include delayed, zero-order release (Figs. 3 and 4), and pulse release (Fig. 5, A and B), as well as combinations thereof.

A. Zero-Order Release Rate

The Port System can release drug at a zero-order release rate alone or in combination with an immediate-release pulse, a sustained-release component, a delay, or a combination of the above. The release of drug is independent of pH and can be designed for both water-soluble and poorly soluble drugs. Referring back to Figures 3 and 4, the zero-order release rate portion is contained in one of the compartments, generally in the capsule body below the sliding separator. The capsule body is nondisintegrating owing to the water-insoluble nature of the semipermeable film coat applied to the capsule body.

Copyright © 2003 Marcel Dekker, Inc.

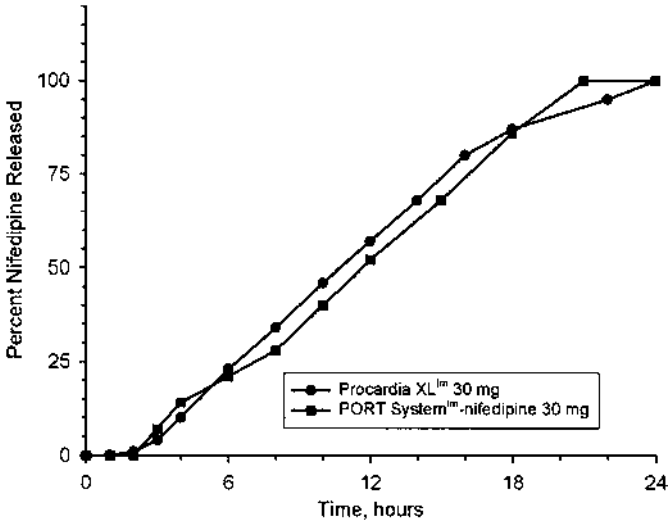


Figure 3 Zero-order release of nifedipine using the Port System compared to Procardia XL™ (30-mg dose). The dissolution apparatus was a USP #2 (VanKel) with paddle speed of 50 rpm, in phosphate buffer, pH 6.8 maintained at 37°C, $n = 3$.

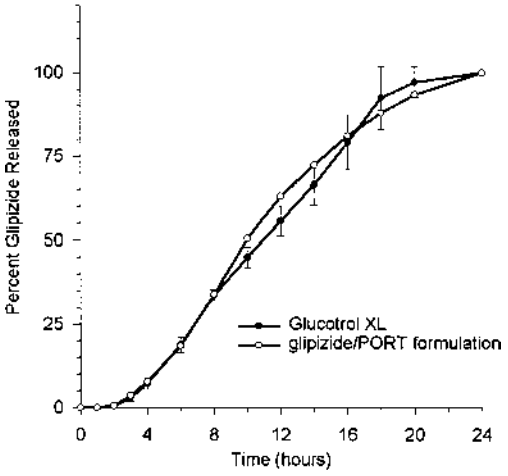


Figure 4 Zero-order release of glipizide using the Port System compared to Glucotrol XL™ (5-mg dose). The dissolution apparatus was a USP #2 (VanKel) with paddle speed of 50 rpm, in simulated gastric fluid (pH 1.2) for 1 h followed by simulated intestinal fluid (pH 6.8) for 24 h, both maintained at 37°C, $n = 3$.

Copyright © 2003 Marcel Dekker, Inc.

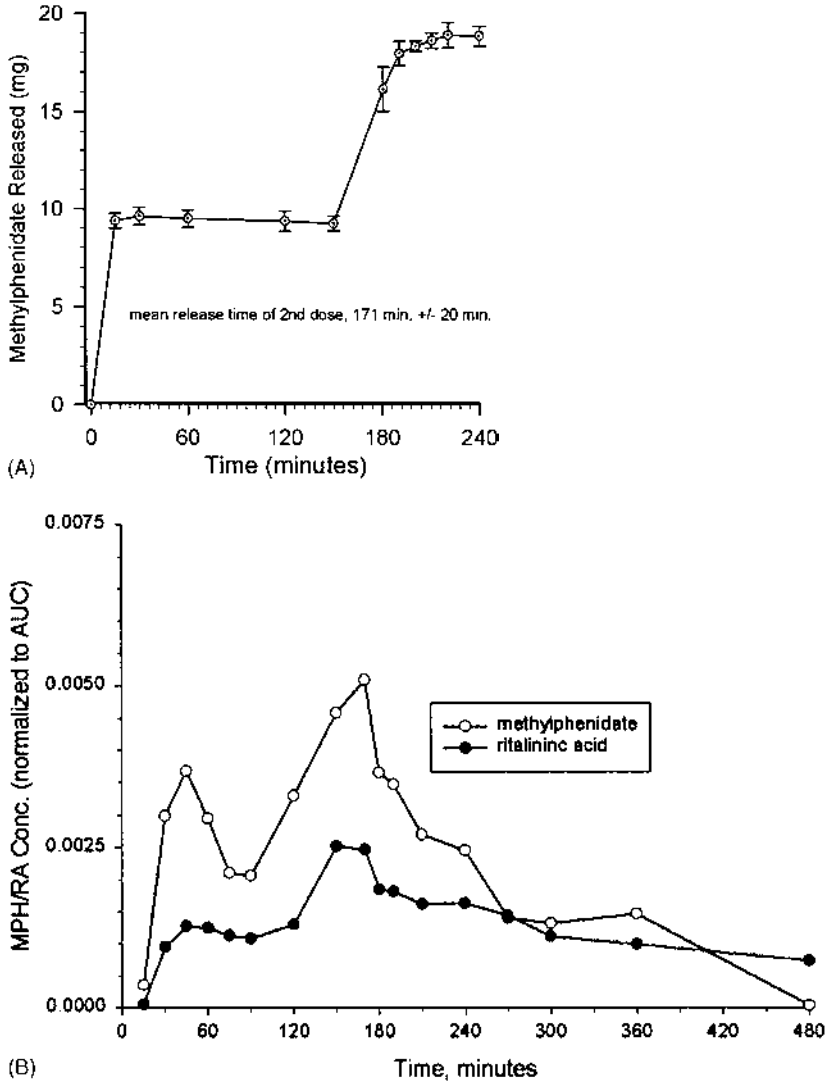


Figure 5 Methylphenidate dosage forms were formulated to release the first dose (10 mg) immediately following contact with fluids and the second dose (10 mg) immediately after 2–3 h. (A) Pulse dosing of methylphenidate in vitro, USP Dissolution Apparatus 2 (VanKel), 50 rpm in simulated gastric fluid, (pH 1.2) for 1 h followed by simulated intestinal fluid (pH 6.8) for 4 h, both maintained at 37°C, $n = 6$. (B) Representative plasma concentrations (divided by the AUC) of methylphenidate and ritalinic acid in the fasted dog model.

Copyright © 2003 Marcel Dekker, Inc.

B. Delayed Release

Unlike enteric coating, the Port System's delayed-release mechanism is pH independent and allows for precise delivery of drug at a given time. Human scintigraphy studies have shown that the gamma emitter samarium chloride releases quickly from the Port System and rapidly disperses through the colon (Fig. 1). The ability of the Port System to achieve complete drug release in the large intestine is due to the dosage form taking up water as it travels through the gastrointestinal tract. As the dosage form reaches the colon, and depending on the solubility of the drug, sufficient water influx has occurred resulting in the partial or complete solubilization of the drug so it is released as a solution. Since the Port System is a specialized container, it can also delay the release of other types of modified-release formulations, such as beads and granules.

C. Immediate- and Delayed-Pulse Release

The Port System can be designed to mimic a twice-a-day dosing interval by putting immediate-release formulations in both the upper and lower compartments (Fig. 5). The resulting formulation is a single unit that releases two doses separated by a time interval of 1–8 h. Either compartment can also be formulated to provide a sustained-release component to accompany the pulse dose.

IV. RESEARCH AND DEVELOPMENT

The Port System has been tested in both animals and humans and shows good in vitro–in vivo correlations for both. The human scintigraphy studies have produced excellent results under both fed and fasted conditions, showing no statistical difference in marker release times between the two.

Compounds of different pharmacological activity tested in the Port System include: vasodilators, anti-inflammatory agents, anticoagulants, antihypertensives, oral hypoglycemic agents, central nervous system agents, decongestants, and nutritional supplements. The Port System is not limited to the chemical structure of the drug and has been tested with neutral and ionizable compounds, proteins, and water-soluble and water-insoluble drugs.

V. REGULATORY ISSUES

All major components of the Port System are of USP/NF or GRAS status and there are no regulatory issues regarding the composition of the dosage form itself.

Copyright © 2003 Marcel Dekker, Inc.

VI. COMPETITIVE ADVANTAGE

The Port System offers the competitive advantage over other technologies in that the rate and the time of drug release can be independently controlled. In addition, multiple drugs and/or release rates can be incorporated into a single unit. The Port System is commercially scalable, leveraging off existing manufacturing technologies for the application of the film coat to the capsule body and the encapsulation process. The encapsulation equipment can be configured to fill powders, granules, pellets, beads, or tablets into the capsule body. Currently, the encapsulation equipment can fill capsule sizes 2–000 and plans are to expand the capsule size range to include sizes 3, 4, and 5. The encapsulation rate ranges from as low as 1000/h to 20,000/h, making it ideal for manufacturing phase 1 clinical supplies or small lots when the API is expensive or in short demand. The wide range in encapsulation rate virtually eliminates scale-up failure since the clinical supplies and commercial lots are manufactured on the same equipment.

The Port System can accept other drug delivery technologies, such as modified-release beads and granules, solubility enhancers, competitive substrates, and permeability enhancers, to improve the bioavailability as well as utilize the client's patented technology to increase patent protection.

VII. CONCLUDING REMARKS

The Port System is a proven drug delivery technology. The versatility of the drug delivery system has application to new chemical entities and line extension of an innovator's product. In addition, the ability to produce a wide variety of release profiles with the technology also makes it possible to achieve bioequivalence for ANDA submissions.

REFERENCES

1. GL Amidon, GD Leesman. Pulsatile drug delivery system. US patent 5,229,131, 1993.
2. GL Amidon, GD Leesman, LB Sherman. Multi-stage drug delivery system. US patent 5,387,421, 1995.
3. GL Amidon, JR Crison. Method for making multi-stage drug delivery system. US patent 5,674,530, 1997.
4. JR Crison, GL Amidon. Method for making multi-stage drug delivery system. US patent 5,976,571, 1999.
5. JR Crison, GL Amidon. Multi-stage drug delivery system. US patent 6,207,191, 1999.

Copyright © 2003 Marcel Dekker, Inc.

22

Pulsincap and Hydrophilic Sandwich (HS) Capsules: Innovative Time-Delayed Oral Drug Delivery Technologies

Howard N. E. Stevens
University of Strathclyde, Glasgow, Scotland

I. INTRODUCTION

Chronopharmaceutical drug delivery [1] is the delivery of drugs in accordance with the circadian rhythms of the disease. The identification of a specific time-dependent "trigger" capable of provoking drug release from an oral formulation after a predetermined time interval represents a significant challenge to the pharmaceutical formulator.

II. PULSINCAP TECHNOLOGIES

Three variants on a capsule theme have been developed that trace their origins back to PolySystems Ltd., a small Scottish company in the late 1980s. The first concept consisted of a device based on the separation of a plug from an insoluble capsule body, which was first described by Rashid [2]. This formulation, which was described in the patent literature, comprised a water-permeable body (Fig. 1) prepared from a water-swellable hydrogel cross-linked polyethylene glycol (PEG) polymer. Depending on their composition, such polymers have the capacity to swell significantly, but in a controlled manner, in aqueous media. A swelling agent (powdered high-swelling polymer) mixed with drug, was filled into the

Copyright © 2003 Marcel Dekker, Inc.

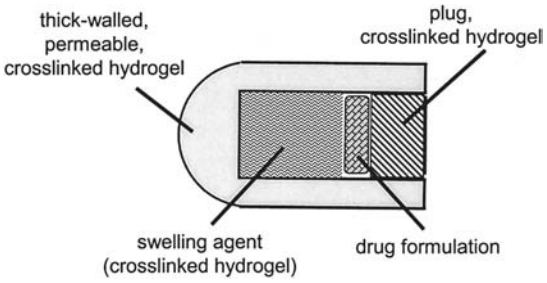


Figure 1 Pulsatile hydrogel capsule [2].

internal cavity of Rashid's molded capsule body and a plug (also of high-swelling polymer) was used to seal the contents into the internal cavity. The rate at which water diffused into the core was controlled by the hydrogel composition and wall thickness of the capsule. The delay period prior to drug release was defined by the time taken for fluid to diffuse through the wall. When fluid came into contact with the capsule contents, the high-swelling polymer absorbed water rapidly, swelled, and caused internal pressure to be generated inside the capsule. This pressure caused the plug to be expelled from the neck of the capsule and drug to be released in a pulsatile manner. Optimization of the construction of the components and the chemistry of the hydrogel polymers enabled time delays to be controlled reproducibly.

A manually prepared prototype formulation with a 5-h lag time was the subject of a pharmacokinetic study in humans designed to release captopril in the colon of the fasted volunteers. Scintigraphic observations confirmed that drug was released from the capsule at the target site; however, pharmacokinetic analysis confirmed that minimal absorption had taken place from the colon [3].

Molding the thermosetting hydrogel polymers required for the capsule body was a very complex process that did not lend itself to industrial scale-up. Further developments of this technology, now more widely referred to as Pulsincap™, were undertaken and improved devices were described in the patent literature [4]. Polysystems was acquired by RP Scherer Corporation in 1990 and the Pulsincap technology was then developed by Scherer DDS Ltd. This second-generation Pulsincap device was less complex than Rashid's earlier capsule and the hydrogel body of the earlier formulation was now replaced by a gelatin capsule, film-coated with ethyl cellulose to render it impermeable (Fig. 2). The link to hydrogel polymer chemistry was retained and a molded hydrogel plug was used to seal the drug contents into the capsule body. In the presence of fluid, the plug swelled at a controlled rate that was independent of the nature or pH of the medium [5].

Copyright © 2003 Marcel Dekker, Inc.

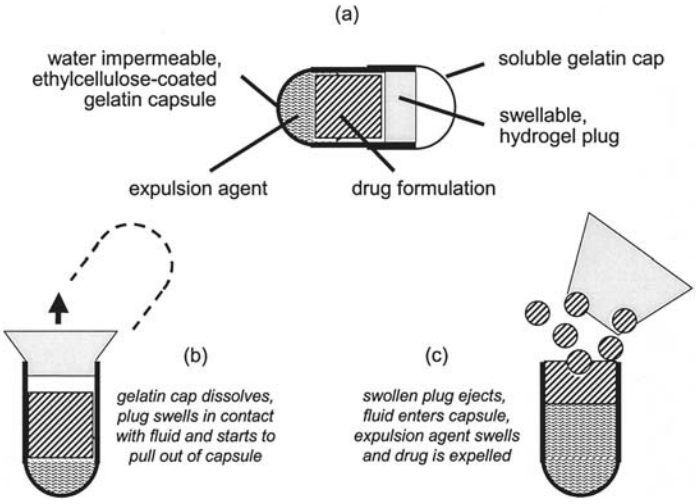

(a)
water impermeable, ethylcellulose-coated gelatin capsule
soluble gelatin cap
swellable, hydrogel plug
expulsion agent
drug formulation
(b)
gelatin cap dissolves, plug swells in contact with fluid and starts to pull out of capsule
(c)
swollen plug ejects, fluid enters capsule, expulsion agent swells and drug is expelled

Figure 2 Pulsincap delivery system [4].

As it swelled, the plug developed a frustroconical shape and slowly pulled itself out of the capsule. The length of the plug and its insertion distance into the capsule controlled the pulse time reliably.

This second-generation Pulsincap formulation has been studied in numerous human volunteer studies (e.g., [6,7]) and was well tolerated in humans [8]. To effect complete drug release from the capsule following plug ejection, an active expulsion system was employed to rapidly and completely expel the contents from the capsule, as demonstrated with delivery of salbutamol to human volunteers, where the expulsion system low-substituted hydroxypropylcellulose (LH-21®, Shin-Etsu) was employed [9,10].

Due to the fact that the mechanism of action was controlled by the plug sliding out of the capsule, a significant factor for the correct operation of Pulsincap was the tightness of fit of the hydrogel plug in the capsule. If the fit of the plug was too slack, it ejected prematurely, whereas when it fitted too tightly, drug was released erratically [11]. To respect the very tight dimensional specifications demanded for predictable operation, each plug was subjected to three-dimensional measurement using laser gauges. As a result of the cost implication of this requirement, the delivery system was never adopted for large-scale human health care applications. However, a low-volume diagnostic test kit, based on Pulsincap releasing nutrient components into a microbial test medium after a 6-h lag time, was commercialized in 1997 (SprintSalmonella™, Oxoid Ltd., Basingstoke, UK).

Copyright © 2003 Marcel Dekker, Inc.

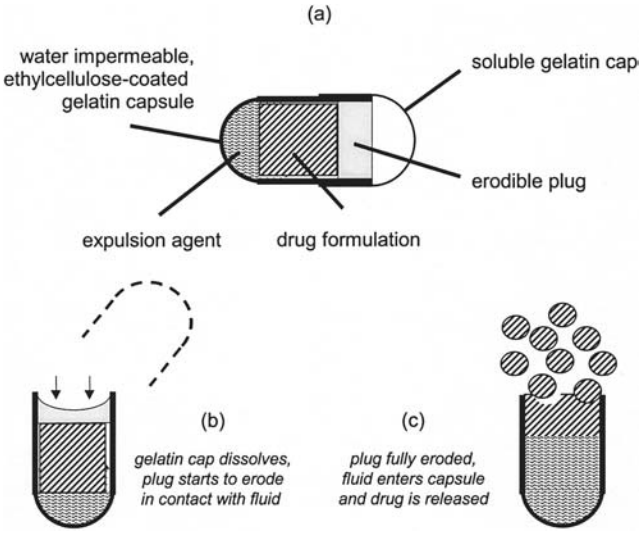


Figure 3 Erodible plug time-delayed capsule [12].

More recent studies have been undertaken on a further simplified adaptation of the technology. Now working at Strathclyde University, Stevens et al. [12] and Ross et al. [13] eliminated reliance on hydrogel polymers and developed a Pulsincap formulation that employed a simple erodible compressed tablet in place of the swelling hydrogel plug (Fig. 3). Since the tablet eroded in place, it did not move relative to the capsule body and this factor overcame the need for the precise dimensional tolerances between plug and capsule required by the sliding mechanism of the plug in the earlier Pulsincap formulations.

A range of erodible tablet formulations was studied using ethyl cellulose–coated gelatin capsule bodies. It was shown that controllable time-delayed release of propranolol could be achieved with pulse time being determined by either plug composition or its thickness. Ross et al. [13] again utilized low-substituted hydroxypropylcellulose (LH-21®, Shin-Etsu) as a swellable expulsion system and achieved release of propranolol over a controllable 2–10-h range using erodible tablet plugs compressed from mixed lactose and HPMC (Methocel®, DOW) excipients.

Krögel and Bodmeier [14] similarly studied the application of erodible plugs fitted in plastic capsules using formulations based on either compressed tablets or congealed semisolid materials. Release of chlorpheniramine after time delays was obtained by manipulating plug composition or weight.

Copyright © 2003 Marcel Dekker, Inc.

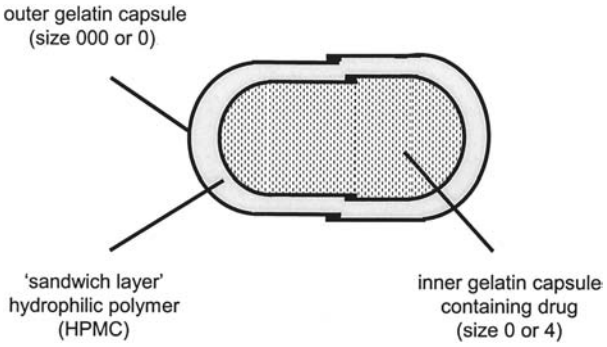


Figure 4 The hydrophilic sandwich capsule [15].

III. HYDROPHILIC SANDWICH (HS) CAPSULE

In an attempt to develop a simple, time-delayed probe capsule, Stevens et al. [15] devised a manually assembled delivery system based on a capsule-within-a capsule, in which the intercapsular space was filled with a layer of hydrophilic polymer (HPMC). This effectively created a "hydrophilic sandwich" between the two gelatin capsules. When the outer capsule dissolved, the sandwich of HPMC formed a gel barrier layer that provided a time delay before fluid could enter the inner capsule and cause drug release. The time delay was controlled by the molecular weight of the polymer and could be further manipulated by the inclusion of a soluble filler, e.g., lactose, in the hydrophilic layer (Fig. 4).

The HS capsule was studied in two configurations, either with an external size 000 capsule and an internal size 0, or a "mini HS," in which the external capsule was size 0 and the internal capsule was size 4. Soutar et al. [16] employed a gastroresistant version of the larger HS capsule in a cohort of 13 volunteers to deliver 500 mg paracetamol to the ileocecal junction/proximal colon. Absorbed drug was monitored using salivary analysis and a mean T_{max} value of 7.9 h (s.d. $\pm$ 0.96) was observed.

IV. CONCLUDING REMARKS

Pulsed drug delivery using systems based on Pulsincap technology and derivatives has been demonstrated in the clinic using scintigraphy. Current research is focused on providing a readily adaptable configuration whose release characteris-

Copyright © 2003 Marcel Dekker, Inc.

tics in vivo can accurately be reflected in compendial in vitro tests. Results so far are extremely encouraging with good concordance in healthy volunteers.

REFERENCES

1. HNE Stevens. Chronopharmaceutical drug delivery. J Pharm Pharmacol 50:S5, 1998.
2. A Rashid. Dispensing device. EP 0,384,642, 1990.
3. IR Wilding, SS Davis, M Bakhshaee, HNE Stevens, RA Sparrow, J Brennan. Gastrointestinal transit and systemic absorption of captopril from a pulsed-release formulation. Pharm Res 9:654–657, 1992.
4. ME McNeill, A Rashid, HNE Stevens. Drug dispensing device. GB patent, 2,230,442, 1993.
5. JS Binns, M Bakhshaee, CJ Miller, HNE Stevens. Application of a pH independent PEG based hydrogel to afford pulsatile delivery. Proc Int Symp Control Rel Bioact Mater 20:226–227, 1993.
6. M Bakhshaee, JS Binns, HNE Stevens, CJ Miller. Pulsatile drug delivery to the colon monitored by gamma scintigraphy. Pharm Res 9(suppl):F230, 1992.
7. JM Hebden, CG Wilson, RC Spiller, PJ Gilchrist, PE Blackshaw, M Frier, AC Perkins. Regional differences in quinine absorption from the undisturbed human colon assessed using a timed release delivery system. Pharm Res 16:1087–1092, 1999.
8. JS Binns, HNE Stevens, J McEwen, G Pritchard, FM Brewer, A Clarke, ES Johnson, I McMillan. The tolerability of multiple oral doses of Pulsincap capsules in healthy volunteers. J Control Rel 38:151–158, 1996.
9. HNE Stevens, JS Binns, MI Guy. Drug expelled from oral delivery device by gas. International patent application WO 95/17173, 1995.
10. HNE Stevens, A Rashid, M Bakhshaee, JS Binns, CJ Miller. Expulsion of material from a delivery device. US patent 5,897,874, 1999.
11. M Hegarty, G Atkins. Controlled release device. International patent application WO 95/10263A1, 1995.
12. HNE Stevens, A Rashid, M Bakhshaee. Drug dispensing device. US patent 5,474,784, 1995.
13. AC Ross, RJ MacRae, M Walther, HNE Stevens. Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. J Pharm Pharmacol 52:903–909, 2000.
14. I Krögel, R Bodmeier. Pulsatile drug release from an insoluble capsule body controlled by an insoluble plug. Pharm Res 15:474–481, 1998.
15. HNE Stevens, AC Ross, JR Johnson. The hydrophilic sandwich (HS) capsule: a convenient time-delayed oral probe device. J Pharm Pharmacol 52:S41, 2000.
16. S Soutar, B O'Mahony, M Bakhshaee, AC Perkins, T Grattan, CG Wilson, HNE Stevens. Pulsed release of paracetamol from the hydrophilic sandwich (HS) capsule. Proc Int Symp Control Rel Bioact Mater 28:790–791, 2001.

Copyright © 2003 Marcel Dekker, Inc.

23

Development of the Egalet Technology

Daniel Bar-Shalom and Lillian Slot
Egalet A/S, Vaerlose, Denmark

Wang Wang Lee and Clive G. Wilson
Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland

I. INTRODUCTION

The use of delayed-release devices to achieve temporal or spatial targeted delivery of actives to the distal human gut is well illustrated by many examples provided in the chapters in this part of the book. The solid oral controlled-release technologies that have proven commercially viable are almost exclusively based upon diffusion, either from a matrix or through a membrane. Since the solvent available in the gastrointestinal tract is water, it follows that water-soluble drugs are handled well by such systems but water-insoluble drugs present almost insurmountable challenges. At this time there is only one system commercially available, namely Oros™ osmotic technology from ALZA, able to deliver water-insoluble drugs capably. This leaves many unmet needs in formulation development, with respect to accommodating labile drugs, providing burst or delayed-release characteristics, and allowing combinations of different drugs in one unit.

Early in the development of the Egalet® technology, it was proposed that a system able to overcome these limitations should be based upon a principle other than diffusion. Modulation of erosion seemed to be a promising avenue to exploit, particularly if the erosion of the matrix was as fast as the penetration of water into the matrix, providing surface erosion control.

Copyright © 2003 Marcel Dekker, Inc.

II. EGALET IN BRIEF

The basic form of the Egalet technology is illustrated in Figure 2. As can be seen from the diagram, the system consists of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. Time of release can then be modulated by the length and composition of the plugs. The shells are made of cetostearyl alcohol and ethylcellulose while the matrix of the plugs comprises a mixture of polyethylene glycol monostearates and polyethylene oxides.

The manufacturing process involves an injection molding step. The premixed powders, which are used to form either the active matrix or plug, are fed into the mold and a reciprocating injection-molding process allows sequential molding of the shell and the core contents within the dies. This design provides an efficient manufacturing process coupled with high accuracy in dimensions and fill.

III. DEVELOPMENT ISSUES IN EGALET TECHNOLOGY

A. Matrix Erosion

The matrix is designed to erode when in contact with available water but, at the same time, it is desirable that water does not diffuse into the matrix until the point of release thus avoiding hydrolysis and diffusion and reducing the effects of luminal enzymatic activity. The two effects might appear to be opposing goals but the objective is to reach a balance where the erosion is as fast as the diffusion of water into the matrix. To ensure a gradual release of the active substance(s), the matrix has to be eroded in a heterogeneous manner, the opposite of homogeneous erosion or erosion occurring simultaneously throughout the matrix [1].

The original idea was to achieve a matrix in which erosion was independent of pH; for this reason polyethylene glycols were tested at an early stage. The nomenclature of poly(ethylene glycols) and poly(ethylene oxides) can be confusing; here PEO/PEG is used as the general term, PEO the nonionic homopolymer of ethylene oxide and PEG for an addition polymer of ethylene glycol and water [2]. In terms of physicochemical properties they are indistinguishable [3]; for the purposes of the present application PEGs have average molecular weights up to 35,000 and PEOs have average molecular weights greater than 100,000.

PEO/PEGs can be melted and cast into solid shapes, as in suppositories. Low-molecular-weight PEGs (up to 6000) made into solid shapes do erode heterogeneously in water, but have low melting points, rendering them impractical for oral dosage forms. High-molecular-weight PEO/PEG solid shapes form gels in water and the gel will either inhibit release of water-insoluble substances or will impede the release of water-soluble ones. It was found that the addition of

Copyright © 2003 Marcel Dekker, Inc.

poly(ethylene glycol) monostearate (PEG-MS) to the higher-molecular-weight PEO/PEGs in the right proportion resulted in solid shapes eroding heterogeneously.

A possible explanation for this effect is that when molten PEO/PEG cools and solidifies, it assumes a structure that is partly crystalline and partly amorphous, with cracks or fissures. Water penetrates rapidly through the fissures and the surface and deeper layers begin to dissolve simultaneously, resulting in gel formation. PEG-MS melted together with PEO/PEG will, when cooled, align so that the PEG portion will blend itself with the PEO/PEG and the MS part will tend to be left on the surface of the particles, rendering the fissures hydrophobic and impassable to water. This results in heterogeneous erosion, because the erosion proceeds layer by layer. This matrix (PEO/PEG, PEG-MS, an optional filler, and different drugs) shows zero-order release in vitro irrespective of pH but directly dependent upon rate of agitation. In some cases the active substances might function at least partly like PEG-MS.

B. Agitation

When tested according to the generic USP dissolution tests (120–150 RPM for 2 h, 30–50 RPM the rest of time) it became apparent that the release in the first 2 h during high agitation was much higher than in the later period of low agitation. Addition of small amounts (less than 10%) of cellulose derivatives of the type used for enteric coatings [cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (HPMCA), hydroxypropylmethyl cellulose succinate] was found to slow down the rate of erosion at low pH but not at near-neutral or basic pH. This effect can be used to modify the relative rates of erosion at different agitations if the given agitation is associated with a particular pH as, for example, in the stomach relative to the small intestine. It is speculated that the properties of the active substances or other materials within the core might fulfill this need.

The effect described illustrates that different materials added to the matrix can have profound effects on the erosion rates and also in the processability of the matrix in production. This is true also for the active compounds, since very water-soluble ones will speed the erosion, whereas water-insoluble ones will slow it (for example, testosterone base will stop it altogether at low concentrations). The pKs of the active compounds can also have a significant effect on the erosion. This is, of course, also true for excipients; cellulose derivatives in general add plasticity. Starch, lactose, sucrose, and mannitol are convenient fillers as they normally have little impact on the release, other than the solubility effect mentioned above. This can be used to compensate for water-soluble or insoluble drugs or to adjust the rate of erosion. Other additives may modify the crystallinity of the matrix or other parameters.

Copyright © 2003 Marcel Dekker, Inc.

C. Geometry

The three-dimensional form of the matrix is all-important as the release is directly proportional to the area eroded. An eroding sphere loses surface at a rate proportional to the radius at the third potency (volume = $4/3 * \pi * r^3$) but a flat slab at a rate nearly proportional to the thickness or height of the slab (volume = length * width * height), and other shapes (for example, a "short macaroni") will exhibit a near-zero-order rate of erosion and thus rate of release. All this is true if the whole surface of the matrix is exposed.

A matrix encased in a tube open at one or both ends will expose the same area to erosion at all times and this will result in zero-order performance. Changing the bore of the tube along its length will modify the release accordingly. The tube can be nonerodible and nondegradable but degradability obviates the con-

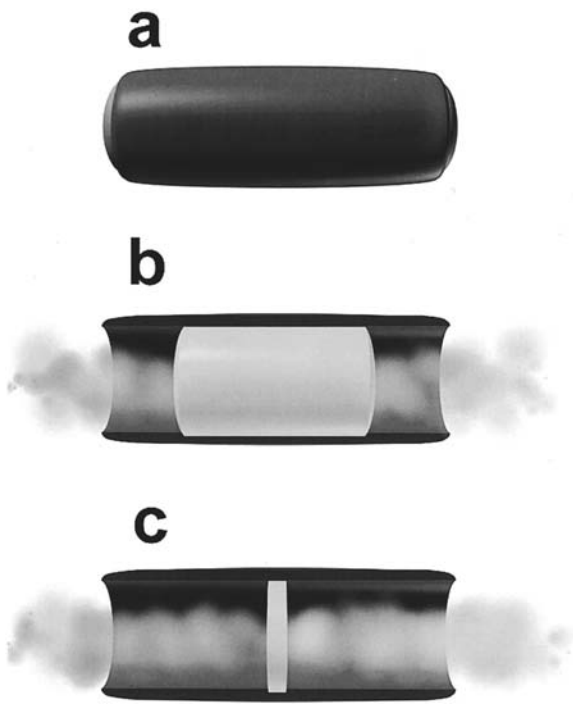


Figure 1 Release from Egalet demonstrating heterogeneous erosion and constant release: (a) whole Egalet, (b) Egalet during erosion, and (c) Egalet showing almost complete erosion. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

cerns about residues in feces and an erodible shell affords yet another element of control of the rate of release.

It is worthwhile observing that two (or more) active substances in a matrix will be released at the same percentile rate per unit of time irrespective of the concentration of each drug, as long as the distribution of the active substances is uniform throughout the matrix (Fig. 1) showing a zero-order, continuous release.

D. Burst Release

The matrix need not be the same in its whole length; it is possible to build a dosage unit with different sections, as illustrated in Figure 2.

In this example we see two identical outer sections, "plugs," enclosing an internal one. If the outer plugs do not contain any active substance, nothing will be released while they erode but when the internal layer is reached, it will release whatever it may contain, the release being immediate or gradual if desired.

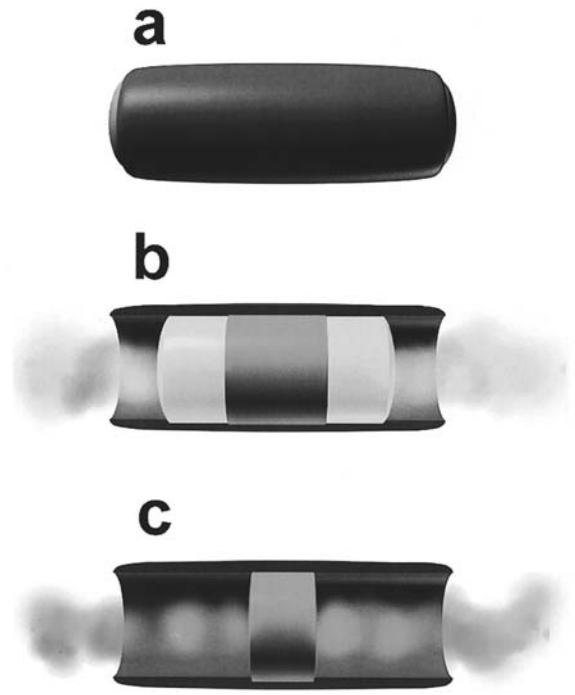


Figure 2 Egalet showing one of many possible variants. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

The outer plugs *may* contain an active substance and this active may or may not be different from the one in the internal section. Variants of this design might include:

1. No drug in the outer plugs to achieve a delay in the onset of the release, useful in evening administration/early-morning dosage or to achieve targeting to a given part of the gastrointestinal tract.
2. Same active substance in the outer and inner plugs but a different concentration, to "tailor-make" a profile.
3. One or more active substances in the outer and one or more in the inner for a combination dosage.

IV. PRODUCTION

The key components of both the tube and matrix are thermoplastic and therefore amenable to injection molding. The potential of injection molding in pharmaceutical production has been recognized, its main advantages being high accuracy of weight and content, reproducibility from batch to batch (although it is best suited to continuous process), and low cost [4]. Upscaling presents few problems as the prototyping and production are often made in identical machines. Figure 3 depicts a flow chart that illustrates a typical process.

V. CLINICAL EXPERIENCE

The device has been used in a number of clinical trials that have aided in the optimization of the configuration. We have also conducted scintigraphy experiments that relate the position of release of active to the plasma concentrations in humans. The results of this study have been published as a communication [5] and further studies are ongoing in a number of centers to address issues relating to dosage form performance. With regard to the regulatory position, there have been no toxicity issues since all ingredients in the Egalet have pharmacopoeia monographs and have been used historically in oral dosage forms.

VI. COMPETITIVE ADVANTAGES/UNIQUE FEATURES

The ability to deliver water-insoluble compounds is probably the most significant feature of the Egalet technology. In addition, the simplicity of the concept and the production method, which is inexpensive and well established, add to its appeal. Active compounds entrapped in the Egalet matrix are protected from

Copyright © 2003 Marcel Dekker, Inc.

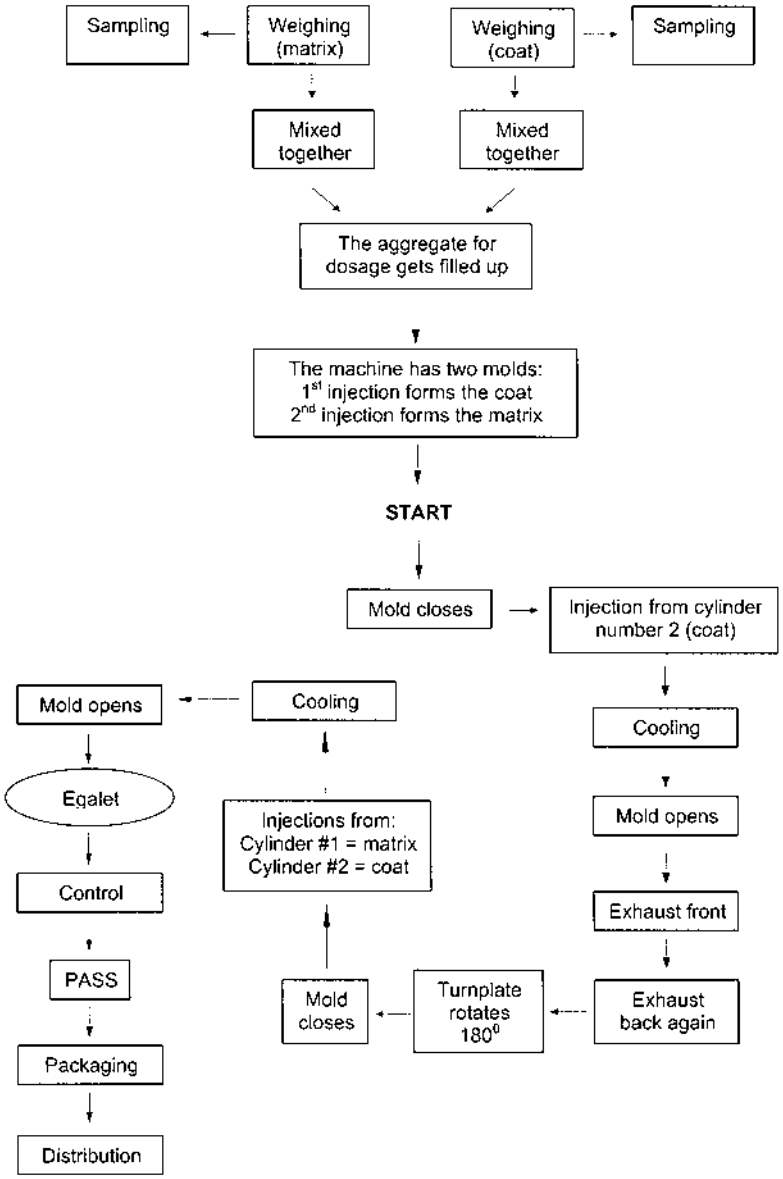


Figure 3 Flow charts showing manufacturing steps in Egalet technology.

Copyright © 2003 Marcel Dekker, Inc.

oxygen and humidity and therefore the technology appears suited for chemically unstable substances.

Combination of actives is a controversial issue but the Egalet technology can deliver two or more substances simultaneously and, in appropriate cases, could be a sound platform for such products. The same holds true with absorption enhancers, cofactors, stabilizers, and other additives. Finally, the stabilization effects coupled with the (modest) ability to deliver to a given section of the gastrointestinal tract open the possibility of peptide delivery via the oral route. In addition, utilization of the Egalet for chronotherapeutic applications offers intriguing prospects for the future.

VII. UNRESOLVED ISSUES

The key components of Egalet, PEG/PEOs, are known to have a few incompatibilities:

1. Certain chemical moieties, notably phenols, are incompatible with PEG/PEOs and lower the melting point of the matrix.
2. Substances with a melting point close to that of the PEG/PEOs will, likewise, lower the melting point of the mixture.

As to the maximum dose that can be delivered from the Egalet technology, the active should, in general, not exceed 50% of the matrix.

VIII. CONCLUDING REMARKS

Although this short description of the technology has concentrated on applications in the field of oral drug delivery, there are other possible alternative routes of use. These include utilization as part of another device, which is not necessarily designed for administration of drugs, e.g., insertion into the urinary bladder mounted on the tip of a catheter. Other routes, such as vaginal delivery, may allow this technology to be used to provide controlled release of actives over several days or even weeks as required.

REFERENCES

1. P Buri. Formes Pharmaceutiques Nouvelles. Paris: Lavosier Technique et Documentation, 1985.
2. USP Pharmacopoeia 24 NF. Published by United States Pharmacopoeial Convention Inc., Rockville, MD, pp. 2493–2497.

Copyright © 2003 Marcel Dekker, Inc.

3. JM Harris. Polyethylene Glycol Chemistry. New York: Plenum Press, 1992.
4. G Cuff, F Raouf. A preliminary evaluation of injection moulding as a tabletting technology. Pharm Tech Eur 4:18–26, 1999.
5. WW Lee, B O'Mahony, D Bar-Shalom, L Slot, CG Wilson, PE Blackshaw, AC Perkins. Scintigraphic characterisation of a novel injection moulded dosage form. Proc Int Symp Control Rel Bioact Mater 27: 1288–1289, 2000.

Copyright © 2003 Marcel Dekker, Inc.

24
The Enterion Capsule

David V. Prior, Alyson L. Connor, and Ian R. Wilding*
Pharmaceutical Profiles Ltd., Nottingham, England

I. INTRODUCTION

Advances in combinatorial chemistry, proteomics, and genomics have led to the potential for an unprecedented number of new molecular entities (NMEs) to enter full-scale development. Although the emphasis remains focused on developing oral products, few drug candidates have ideal biopharmaceutical properties for oral administration (Table 1) [1]. Pharmaceutical companies have therefore recognized the need to identify those compounds with problematic biopharmaceutical properties long before the first formal, prototype formulations are administered to humans [2]. As a consequence, drug discovery groups now routinely screen potential clinical candidates for poor aqueous solubility and permeability.

A wide range of different techniques are currently available to conduct such screening studies, including a variety of in silico, in vitro, and ex vivo technologies as well as the more traditional live animal models. Although some of these technologies may be well suited to high throughput screening (HTS), output predictions are far from definitive and need to be treated with caution. Increasingly therefore, pharmaceutical and drug delivery companies are using human drug absorption (HDA) studies to provide a more reliable "route map" for development of selected NMEs. Such studies are now easily conducted during early-phase development using specially designed, engineering-based capsules to provide noninvasive, targeted drug delivery to key sites of the human gut. The most advanced technology in this arena is the proprietary Enterion™ capsule (Phaeton Research, Nottingham, UK), which is emerging as the market leader. This device

* Corresponding author.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 "Ideal" Biopharmaceutical Properties for Oral Drug Delivery [1]

Aqueous solubility to allow a single dose to dissolve in 100–400 mL of water
Apparent log P of circa 2
Little first-pass metabolism
Terminal half-life appropriate for likely (once-a-day?) dosing regimen

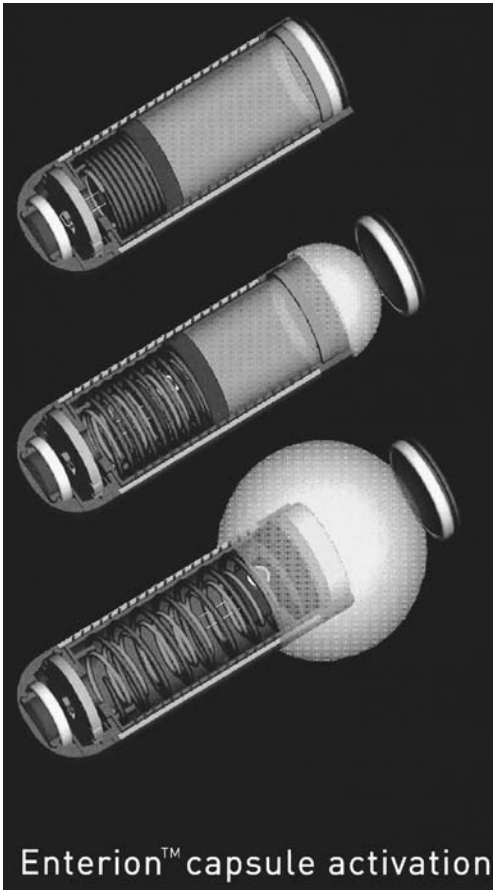


Figure 1 Enterion capsule activation. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

is extremely versatile and capable of delivering a wide variety of formulations, including solutions, viscous suspensions, particulates, pellets, and minitablets.

To track the gastrointestinal transit of the Enterion capsule, a radioactive marker is placed inside a separate sealed tracer port to allow real-time visualization using the imaging technique of gamma scintigraphy. When the capsule reaches the target location, it is remotely triggered by external application of an oscillating magnetic field. The capsule contents are then actively ejected in rapid bolus fashion (Fig. 1). Upon activation the capsule emits a confirmatory radio frequency signal, which may be used as a positive indicator to begin the blood-sampling protocol.

Pharmacokinetic data generated in this way allow a direct relationship to be established between human drug absorption and the intestinal site of delivery. Such information can be extremely valuable, especially for complex molecules, when selecting appropriate drug development strategies and "enabling technologies."

II. HISTORICAL DEVELOPMENT

Historically, the most popular approach for determining the absorption of drugs from different regions of the intestine has been through the use of perfusion or intubation techniques [3–5]. These techniques require invasive tubes to be placed at the relevant part of the gastrointestinal (GI) tract via the mouth or rectum. Once located at the correct region, a drug solution or suspension is infused into the gut lumen at a predetermined rate. Clearly these invasive procedures are associated with significant discomfort and, more importantly, the presence of a tube in the intestines has been demonstrated to alter the function of the GI tract [6]. In particular, intubation has been shown to influence the absorption and secretion balance within the gut, which questions the pharmaceutical relevance of drug absorption data collected via this approach.

Over the last 20 years, a number of engineering-based capsule devices have been developed to allow collection of human absorption data in a noninvasive manner [7]. The primary emphasis of these different systems has been the ability to control the time and location of drug release. Below is a summary of the operative mechanisms for each of the commercially available technologies that preceded the Enterion capsule.

A. High-Frequency (HF) Capsule (Battelle-Institute V, Frankfurt am Main, Germany)

Release of drug from the HF capsule, which was developed in the early 1980s, is triggered by a radiofrequency (RF) pulse from a high-frequency generator ex-

Copyright © 2003 Marcel Dekker, Inc.

ternal to the body [8,9]. Heat generated as a result of the RF-induced current melts a thread and releases a needle, which in turn pierces a latex balloon allowing its contents to passively empty from ports in the wall of the capsule.

Unfortunately, this device was not well suited to particulate formulations owing to the difficulty of filling powders into the balloon. The passive release mechanism also means that there is a reasonable chance of incomplete in vivo drug release from the balloon. The use of X-ray fluoroscopy to track the position of the capsule has further limited its application because of the potential for a high dose of radiation during studies targeting colonic absorption.

B. Gastrotarget Telemetric Capsule (Gastrotarget Corp, Tonawanda, NY)

The Gastrotarget telemetric capsule has a complicated mode of action [10]. Activation is triggered by an external RF pulse, which releases a membrane. A needle then punctures the membrane causing reagents to mix and liberate carbon dioxide gas. The resulting pressure increase drives a piston, which in turn dislodges a plug and empties the 200 μL contents. In vivo drug release is confirmed by detection of a dosing indicator signal.

With this system, location in the GI tract is estimated by administering a dummy capsule on the day prior to dosing. This has the obvious disadvantage of introducing study inefficiencies and volunteer inconvenience. Furthermore, there is significant potential for error since GI transit time may vary even over 24 h.

C. Telemetric Capsule (INSERM U61, Strasbourg Cedex, France)

The Telemetric capsule contains a location detector, transmitter, lithium battery, and interchangeable drug reservoir tip [11]. As a consequence, it is the bulkiest of the devices at 39 mm in length and weighing 3.5 g. With the tracking cogwheel exposed, the capsule expands to a width of 20 mm, which presumably explains reports of prolonged stomach retention. Unfortunately, the activation mechanism has a high current drain limiting the device to only 8 h of operation, although this could be extended with developments in battery technology.

Activation is triggered by an external magnet, which operates a magnetic switch within the capsule to connect the battery to a microfurnance. This, in turn, breaks a plastic strip, which releases a previously compressed spring to clear the aspiration orifice. The drug reservoir is under vacuum and so the capsule contents, in the form of a solution, are immediately forced out. Again with this device, particulate delivery is made difficult by the narrow release orifice.

Location of the capsule in the small bowel is estimated by rotation of the cogwheel as a measure of transit distance. This information is transmitted from

Copyright © 2003 Marcel Dekker, Inc.

the capsule and interpolated externally by the investigator. While this tracking approach has the advantage of avoiding any radiation dose, it is of doubtful accuracy given the intersubject variability in intestinal anatomy.

D. InteliSite Capsule (Innovative Devices, Raleigh, NC)

In recent years, the InteliSite® capsule has become a popular research tool for collection of absorption data [12]. It is 10 mm in diameter and 35 mm in length consisting of an onboard electronics/actuator assembly, a drug reservoir 0.8 mL in volume, and a radiotracer port. The outer and inner sleeves of the assembled capsule both incorporate two rows of three apertures spaced around the circumference at 120° increments. The upper compartment of the inner sleeve holds the actuator mechanism, which comprises two shape memory alloy (SMA) wires bent to a predetermined configuration. These SMA wires are preconditioned to straighten in response to an increase in temperature, and are positioned in contact with an aluminium thermal transfer plate. Application of an external oscillating magnetic field induces an electric current in a three-dimensional array of receiving coils, which slowly warms the transfer plate. The torque provided by the resulting straightening of the SMA wires brings about rotation of the inner sleeve to align the inner and outer apertures. Upon alignment, the contents of the drug reservoir are exposed to the luminal fluids allowing for subsequent passive release of the reservoir contents. The location of the capsule is tracked using a gamma camera via a radionuclide placed inside a sealed radiotracer port prior to administration.

However, a number of design limitations with InteliSite have compromised its reliable use in commercial studies. One such problem is the potential for gradual, preactivation leakage of liquid formulations (especially those having a low surface tension) caused by a poor seal between the inner and outer sleeves of the capsule. Furthermore, like other passive-based technologies, the lack of free water and agitation in the distal bowel does not favor complete and reproducible delivery of particulate formulations [13]. Finally, the activation process requires a relatively high input of energy to warm the transfer plate and straighten the SMA wires, resulting in typical activation times in excess of 2 min. However, if the capsule is particularly deep in the body, then activation may take even longer causing the target site to be missed or perhaps fail altogether owing to attenuated input power.

III. DESCRIPTION OF THE TECHNOLOGY

The Enterion capsule has been specifically designed to overcome the limitations of the earlier technologies [14]. It is a round-ended capsule, 32 mm in length and 11 mm in diameter, with a drug chamber of approximately 1 mL in volume

Copyright © 2003 Marcel Dekker, Inc.

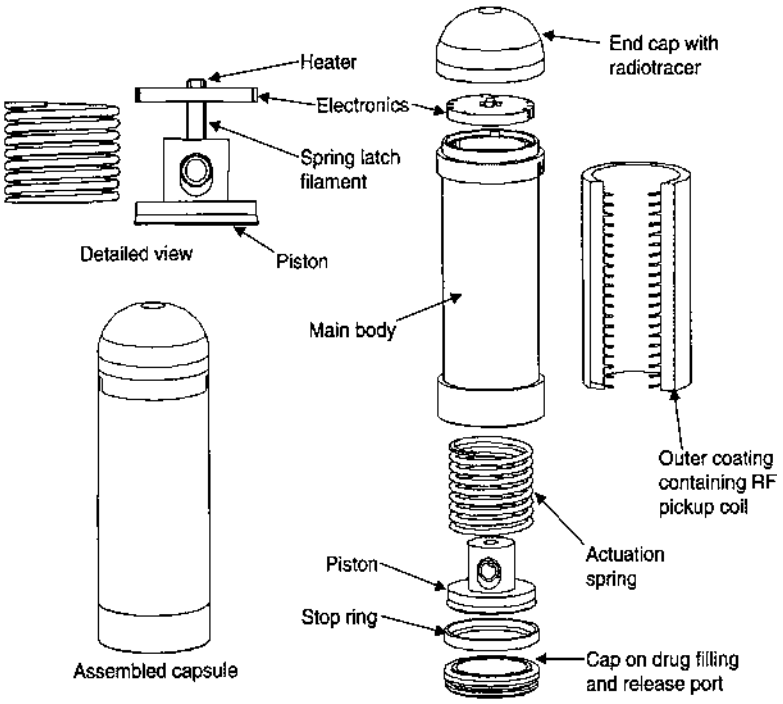


Figure 2 The Enterion capsule and its constituent components.

located within the main body (Fig. 2). The active delivery mechanism makes this technology extremely versatile and fully effective with a wide variety of formulations, including solutions, viscous suspensions, particulates, pellets, and minitablets.

The capsule is loaded with the drug (or drug formulation) through an opening 9 mm in diameter, which is then sealed by inserting a push-on cap with a silicone O-ring gasket. The floor of the drug chamber is a piston face, which is held back against a compressed actuation spring by a high-tensile-strength polymer filament (the spring latch). To track capsule location after administration, a radioactive marker is sealed inside a separate radiotracer port beneath the rounded end cap. This allows the capsule position to be followed in real time using a gamma camera.

When the capsule arrives at the target site in the GI tract, it is remotely triggered by application of an oscillating electromagnetic field, which is generated over the abdominal cavity by an external radiofrequency (RF) generator. The frequency of the field has been optimized at 1.8 MHz, which is low enough for

Copyright © 2003 Marcel Dekker, Inc.

negligible absorption of energy by the body tissues, but sufficiently high to induce usable power in a tuned coil receiver (pickup coil) embedded inside the wall of the capsule. The electric current induced by the magnetic field in the receiving coil is fed to a low-power (0.0625 W) heater resistor, which is situated within a sealed electronics compartment. The small size of the heater (<1 mm^3) results in a rapid temperature rise in just a few seconds.

The spring latch filament that anchors the piston is in direct contact with the heater. As rapid heat buildup occurs, the filament quickly reaches a critical temperature at which point it softens and immediately breaks under the tensile strain of the spring. The energy stored in the spring is only about 0.18 joules; however, the relatively low mass and friction coefficient of the piston produces a high acceleration. Therefore, once the spring is released, it drives the piston into the drug chamber and the corresponding increase in pressure forces off the O-ring sealed cap; this force is rapidly dissipated as the cap is immediately immersed in the relatively viscous GI luminal fluids. Under the continued forward motion of the spring-driven piston, the entire capsule contents are actively expelled into the surrounding GI environment within milliseconds. A restraining (or stop) ring situated near the end of the capsule stops the piston movement. This also maintains the seal and so prevents contact of the electronic components with GI fluids.

As the piston travels the first centimeter immediately after activation, it operates a switch diverting the incoming electrical energy from the heater resistor to a radiofrequency transmitter coil (also embedded inside the capsule wall). This generates a weak radio signal at approximately 500 kHz, which is picked up by an external aerial. Detection of the radio signal confirms that the capsule has opened successfully and so may be used to initiate the blood-sampling protocol.

A more in-depth technical description of the Enterion capsule is provided in two published patent applications, which embody both the capsule [15] and the unique features of the cap release mechanism [16].

IV. RESEARCH AND DEVELOPMENT

A. Design and Fabrication

Phaeton Research developed the Enterion capsule in collaboration with PA Consulting Group, Melbourn, Hertfordshire, UK. The primary challenge was to overcome the so-called "Achilles heel" of preceding technologies and ensure reliable delivery of both liquid and particulate formulations, especially to the distal colon where there is minimal free water to assist passive drug delivery. It was also important to maximize the volume ratio of the drug chamber to that of the overall capsule. This again was intended to provide maximum versatility, while also ensuring that subjects could swallow the capsule relatively easily without any

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Key Design Features of the Enterion Capsule

Essential attribute	Enterion design feature
Biocompatible	Food contact and medical grade plastics used for fabrication of all parts that come into contact with GI-luminal fluids
Readily swallowed by volunteers	Round-ended with overall dimensions (32 mm × 11 mm in diameter) comparable to 000-sized gelatin capsule
Easy tracking of capsule location	Short half-life radionuclide sealed inside a radiotracer port allows tracking via a gamma camera
Suitable for delivering a range of physical forms	Spring-driven piston ensures rapid and complete delivery of particulate, semisolid, and liquid formulations
High loading capacity	Drug chamber approximately 1 mL in volume
No drug leakage prior to activation	Compressed silicone O-ring provides a reliable closure system with high seal integrity
Reliable activation at all intestinal sites	Compressed spring provides an onboard energy source; RF activation frequency selected to avoid absorption by human tissue; proprietary cap release mechanism based on a unique "rolling" O-ring design
Feedback signal to confirm drug delivery	RF signal generated on forward motion of the piston

serious discomfort or gag reflex. A summary of the essential attributes and how these were achieved through the design and fabrication of the Enterion capsule is presented in Table 2.

B. "Proof of Concept" Clinical Study

A first human trial was undertaken once the capsule development had reached the stage of an advanced prototype. The purpose was to prove the design concept and test the reliability of delivery performance before scaling up the capsule assembly process. In particular, the study was designed to confirm (a) robustness of the closure system and integrity of the O-ring seal during transit, (b) activation of the capsule in different regions of the GI tract, (c) reception of the opened signal, and (d) efficient and complete delivery of both particulate and liquid formulations.

The model drug oxprenolol was selected for the study since it is known to be well absorbed from the human colon [17,18]. An 80-mg dose was loaded into the drug chamber, either as a crushed (powdered) Trasicor® (Novartis) tablet or as 0.8 mL of an aqueous 100 mg/mL solution. A radioactive marker (4 MBq of ^{99m}Tc-DTPA) was mixed with the capsule contents and a second radiolabel

Copyright © 2003 Marcel Dekker, Inc.

(1 MBq of ^{111}In-chloride) was placed inside the separate radiotracer port. Using this dual-isotope scintigraphic technique, it was possible to both track the real-time position of the capsule (^{111}In channel) and visually observe delivery of capsule contents (^{99m}Tc channel).

The powder- and solution-filled capsules were administered to two groups of four healthy male subjects in a parallel study design. The ascending colon was selected as the main anatomical site for drug delivery. However, to ensure a wide range of environments in this first human trial, one capsule was also activated in the stomach, distal small bowel, hepatic flexure, and transverse colon. No adverse events associated with capsule activation were reported and all capsules were retrieved following defecation for visual examination.

Preactivation blood samples were taken every 2 h from the time of dosing and postactivation blood samples were collected over 24 h. Plasma concentrations of oxprenolol were determined using a highly sensitive LC-MS-MS assay. Representative pharmacokinetic (PK) profiles for colonic activation of a powder- and solution-filled capsule are presented in Figure 3.

The preactivation blood samples provided evidence of a robust and reliable seal. The postactivation scintigraphic images showed rapid dispersal of the capsule contents and inspection of the defecated capsules confirmed complete delivery with the piston properly resting against the restraining ring. The PK data following colonic delivery (e.g., Fig. 3) were consistent with rapid bolus delivery of the solution formulation. However, the rate of absorption (as evident from C_{max}) was somewhat reduced for powder delivery despite a comparable $AUC_{0\text{-}24}$. This presumably reflects the lack of free water for drug dissolution in the colon and so demonstrates the power of the technology to distinguish between permeability and solubility limited bioavailability.

C. Commercial Manufacturing

Following the successful "proof of concept" study, the Enterion capsule manufacturing process was transferred from PA Consulting to Hansatech Ltd., Cambridge, UK. Capsules are assembled under an ISO9002 Quality System. Each unit is individually serialized, and throughout assembly, a comprehensive series of electronic and mechanical quality control checks are performed to challenge the critical performance attributes and ensure the proper functionality of every device.

D. Application of the Technology

HDA studies using the Enterion capsule are performed exclusively by Pharmaceutical Profiles (Nottingham, UK), an early-phase development company specializing in the use of imaging technologies to aid decision making. From launch

Copyright © 2003 Marcel Dekker, Inc.

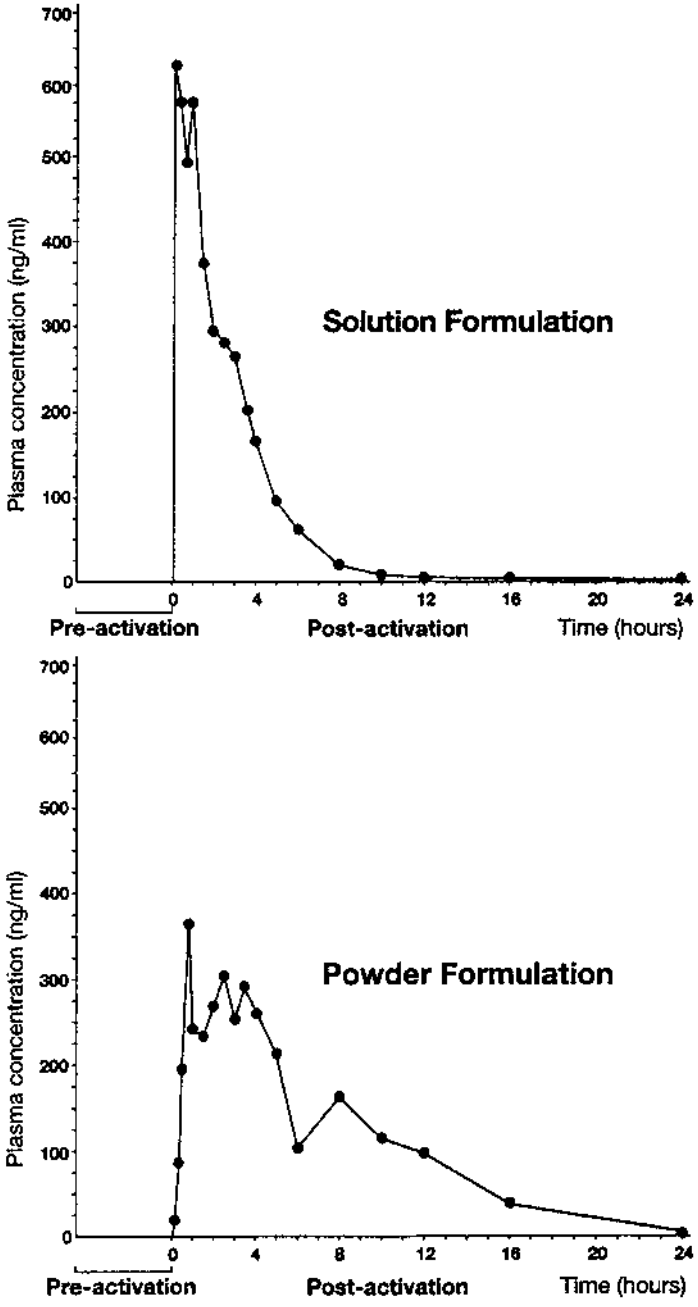


Figure 3 Example pharmacokinetic profiles for oxprenolol 80 mg delivered to the colon as either a powder (subject 4) or solution (subject 7) using the Enterion capsule.

Copyright © 2003 Marcel Dekker, Inc.

of the technology (March 2000) to the time of this writing (April 2002), more than 700 capsules have been dosed and activated successfully to nearly 300 individual subjects. Table 3 presents the cumulative use statistics for the capsule, illustrating its excellent versatility and reliability.

Most HDA studies are sponsored by major pharmaceutical companies and involve proprietary, early-phase compounds; hence opportunities to publish study findings are rare. However, the results of a recent collaboration with Bayer AG (Wuppertal, Germany) to investigate the absorption of faropenem daloxate (FD) have been published [19].

FD is a novel ester prodrug of faropenem sodium, a synthetic broad-spectrum oral antibiotic. After oral administration, FD is rapidly absorbed and hydrolyzed in serum to the active moiety faropenem (FAR). The study was designed to compare the bioavailability of FD when delivered to the proximal small bowel (PSB), distal small bowel (DSB), and ascending colon (AC) versus the immediate-release (IR) tablet. A single dose (equivalent to 300 mg FAR) was administered in a randomized, four-way crossover study in eight healthy male subjects. The Enterion capsule was loaded with a powder formulation (i.e., crushed IR tablet). To further assist with real-time interpretation of each subject's GI anatomy, the water used to administer the Enterion capsule was radiolabeled with ^{99m}Tc-DTPA solution (4 MBq). Following confirmation of capsule activation, blood samples were taken over 24 h and subsequently analyzed using a validated HPLC method with ultraviolet detection.

Table 3 Cumulative Use Statistics for the Enterion Capsule

Use statistic	Cumulative number of Enterion capsules
Subjects dosed	281
Capsules activated in vivo	711
Capsules activated by anatomical region	
Stomach	90 (13%)
Proximal small bowel	121 (17%)
Distal small bowel	214 (30%)
Ascending colon	184 (25%)
Hepatic flexure	61 (9%)
Transverse colon	31 (4%)
Splenic flexure	9 (1%)
Sigmoid colon	1 (0.1%)
Capsules activated by formulation type	
Powder/particulate	306 (43%)
Semisolid paste/gel	32 (5%)
Solution/suspension	373 (52%)

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Pharmacokinetic Parameters of Faropenem (free acid) Following Targeted Delivery of Faropenem Daloxate in Particulate Form Using the Enterion Capsule [geometric mean (geometric SD)]

PK parameter (free acid)	IR tablet formulation	Proximal small intestine	Distal small intestine	Ascending colon
AUC (mg/h/L)	25.80 (1.12)	22.70 (1.17)	20.13 (1.17)	8.64 (1.72)
C_{max}	15.30 (1.44)	11.79 (1.25)	9.96 (1.21)	2.29 (1.65)

The PK profiles following delivery to the PSB and DSB were similar and comparable to the IR reference tablet (Table 4 and Fig. 4). The relative bioavailabilities (AUC) were 87% and 80%, respectively. Significant colonic absorption was also demonstrated for all subjects following delivery to the AC; however, AUC and C_{max} were markedly reduced to 31% and 15%, respectively. These results were considered essential in predicting the optimal FD modified-release profile and in guiding future product development.

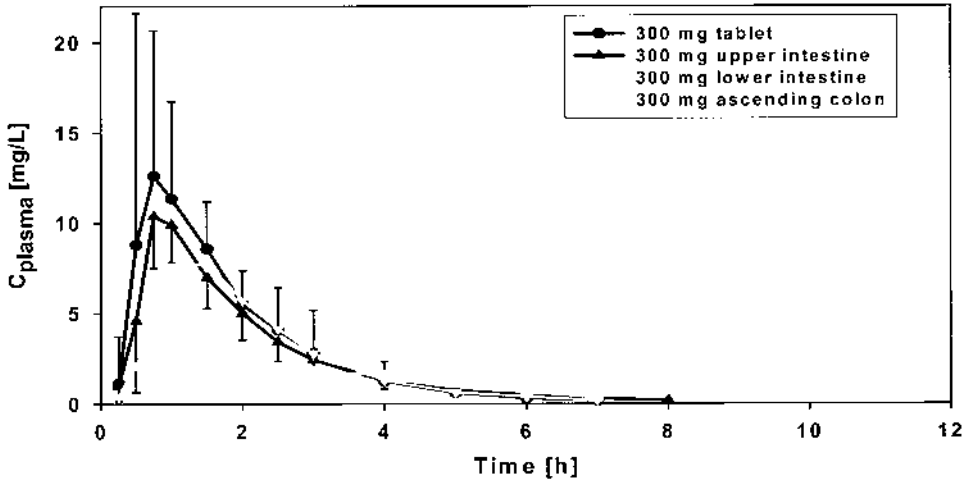


Figure 4 Faropenem (free acid) plasma concentration versus time profiles (geometric mean/SD) 300-mg tablets versus capsule formulation ($n = 8$).

V. REGULATORY ISSUES

The Enterion capsule was originally developed as a research tool. The current version is not intended for any medical treatment or diagnostic purpose and, as

Copyright © 2003 Marcel Dekker, Inc.

such, is not subject to medical device regulations. To date, the capsule has been used exclusively for phase I clinical studies conducted at Pharmaceutical Profiles' facility in Nottingham, UK. All such studies require review and approval by a local ethics committee, which has independently reinforced positive opinion of the capsule's general safety and performance characteristics.

In the future, studies may also be performed in the United States. To satisfy Food and Drug Administration requirements, a comprehensive package of design, development, and previous human exposure information has been compiled in readiness for supplementing any Investigative New Drug (IND) application.

VI. TECHNOLOGY POSITION

HDA studies are increasingly being used in early drug development to rationalize possible strategies for oral drug delivery. Today, the following barriers to successful product development are regularly encountered and so illustrate situations when an HDA study should be considered.

A. Extended Release (ER)

The total transit time for most solid dosage forms in the human GI tract is about 24 h; however, almost 80% of this time will be spent in the colon rather than the small bowel [20]. It is therefore integral to the development of an ER product to have a fundamental understanding of the drug's absorption from the key intestinal regions (e.g., proximal jejenum, terminal ileum, and colon). Compounds shown to be poorly permeable in regions other than the proximal small bowel are unlikely to be viable candidates for traditional slow-release matrix or multiparticulate technologies and may instead dictate formulation of an effective gastroretentive system.

B. Poor Aqueous Solubility

Many NMEs are known have poor aqueous solubility (a trend likely to continue [21]) and often require application of an "enabling technology" to improve bioavailability. Examples of such technologies include the preparation of stabilized nanoparticles to enhance dissolution rate or the formation of liquid or solid solutions (and/or microemulsions) to enhance intrinsic in vivo solubility. HDA studies are especially valuable for screening potential enabling technologies and can indicate the preferred development approach.

C. Biotechnology Compounds

Peptides, proteins, and genomic drug candidates tend to be of high molecular weight and low intestinal permeability and are almost always rapidly degraded

Copyright © 2003 Marcel Dekker, Inc.

in the gut. Chemical enhancer systems designed to alter transcellular absorption have been reported, along with approaches that can specifically alter the tight junctions between cells to facilitate paracellular uptake [22]. HDA studies provide a straightforward and convenient methodology to challenge the oral delivery potential of biotechnology compounds. If negative results are obtained, a prompt decision can be made to either reengineer the compound or explore alternative routes of delivery.

D. Intestinal Metabolism and Efflux

An increasing number of NMEs demonstrate not only complex chemistry, but also low and highly variable pharmacokinetics. CYP 3A4 gut-wall metabolism in combination with intestinal transporter systems (of which pg-P is the best known) is now thought to play an influential role and can provide major development obstacles for NMEs [23]. As more transporter systems are discovered, a growing number of companies are attempting to develop technologies designed to inhibit intestinal metabolism and/or efflux. HDA studies can be used to identify susceptible compounds to intestinal metabolism/efflux and evaluate excipients capable of influencing the process.

VII. FUTURE DIRECTIONS

A likely next generation of the Enterion technology is an extended (or perhaps programmable) release version, so that drug can be infused more slowly or pulsed to deliver to different intestinal regions. Future versions could even include an onboard miniaturized video camera and/or a system for collecting samples of luminal fluid.

The technology also has potential as a high-tech medical or diagnostic device for targeted delivery of therapeutic or diagnostic agents to very specific regions of the intestine. Possible indications would include disease states requiring highly localized topical treatment, such as some colon cancers.

REFERENCES

1. SL Krill. The Drug Delivery Companies Report. Pharma Ventures. Oxford, England, 2000, pp. 43–45.
2. ES Prosser. The road to drug delivery. Chem Ind 19:632–634, 2000.
3. N Rouge, P Buri, E Doelker. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm 136:117–139, 1996.

Copyright © 2003 Marcel Dekker, Inc.

4. L Knutson, B. Odlind, R Hullgren. A new technique for segmental jejunal perfusion in man. Am J Gastroenterol 84:1278–1284, 1989.
5. H Lennernäs, O Ahrenetet, R. Hallgren, L Knutson, M. Ryde, LK Paalzow. Regional jejunal perfusion, a new in vivo approach to study oral drug absorption in man. Pharm Res 9:1243–1251, 1992.
6. NW Read, MN Al Janabi, TE Bates, DC Barber. Effect of gastrointestinal intubation on the passage of a solid meal through the stomach and small intestine in humans. Gastroenterology 84:1568–1572, 1983.
7. D Gardner, R Casper, F. Leith, IR Wilding. The InteliSite capsule: a new easy to use approach for assessing regional drug absorption from the gastrointestinal tract. Pharm Technol 21:82–89, 1997.
8. U Fuhr, AH Staib, S Harder, K. Becker, D. Liermann, G. Schollnahmmer, IS Roed. Absorption of ipsapirone along the human gastrointestinal tract. Br J Clin Pharm 38:83–86, 1994.
9. H Bode, E Brendel, G Ahr, U Furh, S Harder, AH Staib. Investigation of nifedipine absorption in different regions of the human gastrointestinal (GI) tract after simultaneous administration of ^{13}C- and ^{12}C-nifedipine. Eur J Clin Pharmacol 50:195–201, 1996.
10. JJ Schentag, DT D'Andrea. Telemetry capsule and process. US patent 5,279,607, 1994.
11. A Lambert, F Vaxman, F Crenner, T Wittmann, JF Grenier. Autonomous telemetric capsule to explore the small bowel. Med Biol Eng Comput 29:191–196, 1991.
12. RA Casper, LM McCartney, WJ Jochem, AF Parr. Medical capsule device activated by radiofrequency (RF) signal. US patent 5,170,801, 1992.
13. V Mummaneni, W Doll, E Sandefer, R Page, J Ryo, F Digenis, S Kaul. Gamma scintigraphic evaluation of the intestinal absorption of stavudine in healthy male volunteers using InteliSite capsule. Pharm Sci 1:S-608, 1999.
14. IR Wilding, PH Hirst, AL Connor. Development of a new engineering-based capsule for human drug absorption studies. Pharm Sci Technol Today 3:385–392, 2000.
15. PJ Houzego, DJ Westland, PN Morgan, IR Wilding, PH Hirst. An ingestible device. PCT patent publication WO 01/45789 A2, 2001.
16. PJ Houzego, DJ Westland, PN Morgan, IR Wilding, PH Hirst. Ingestible device for the release of substances at district locations in alimentary canal. PCT patent publication WO 01/45552 A1, 2001.
17. SS Davis, N Washington, GD Parr, AH Short, VA John, P Lloyd, SM Walker. Relationship between the rate of appearance of oxprenolol in the systemic circulation and the location of an oxprenolol Oros 16/260 drug delivery system within the gastrointestinal tract as determined by scintigraphy. Br J Clin Pharmacol 26:435–443, 1988.
18. R Groning, S Weyel, E Akala, E Minkow, N Lambow. Computer-controlled release of oxprenolol from capsules using small gas producing cells and electronic circuits. Pharmazie 54:510–512, 1999.
19. AL Connor, HA Wray, B Voith, U Voigt, J Nagelschmitz, J Kuhlmann, IR Wilding. Using the Enterion capsule to investigate the absorption of faropenem daloxate delivered in particulate form from different sites in the gastrointestinal tract. Poster presentation. AAPS Annual Meeting, Denver, CO, 2001.

Copyright © 2003 Marcel Dekker, Inc.

20. IR Wilding. Site-specific delivery in the gastrointestinal tract. Crit Rev Ther Drug Carrier Syst 17:557–622, 2000.
21. IR Wilding. In search of a simple solution for complex molecules. Scrip Magazine May:9–11, 2001.
22. G Gwinup, AN Elias, ES Domurat. Insulin and C-peptide levels following oral administration of insulin in intestinal-enzyme protected capsules. Gen Pharmac 22: 243–246, 1990.
23. IR Wilding. Evolution of the Biopharmaceutics Classification System (BCS) to oral modified release (MR) formulations: what do we need to consider? Eur J Pharm Sci 8:157–159, 1999.

Copyright © 2003 Marcel Dekker, Inc.

25
Ophthalmic Drug Delivery

Bernard Plazonnet
University of Auvergne, Clermont-Ferrand, France

I. INTRODUCTION

Modified-release formulations are the Cinderella of the ophthalmic drug family as can be appreciated through reading a compendium [1]. The move from traditional ophthalmic dosage forms toward more sophisticated drug delivery systems has been slow. This is due to the fact that certain prerequisites are necessary for ophthalmic formulations that decrease the degree of freedom for the formulator. These include sterility, absence of local toxicity, tolerance, ease of dispensing, antimicrobial preservation for multidose formulations, and iso-osmolarity for aqueous-based formulations. Moreover, since the eye is exposed to the environment, Mother Nature supplied it with protective mechanisms that contribute to the elimination of small dust particles, insects, foreign bodies, or formulations landing on the surface of the eye. Furthermore, the size of the patient group having ophthalmic diseases (marketplace) is not large. Indeed, it represents just a few percentage of the total therapeutic needs. All these factors have limited the number of innovative ophthalmic modified-release formulations on the market today.

Despite these challenges, there is a clear need for ophthalmic products that offer more therapeutic benefit than simple solutions/suspensions can achieve. For example, anti-infectious agents would benefit from longer residence on the surface of the eye and improved compliance and comfort. These could be achieved by the development of a once-a-day formulation. To some extent this has been achieved by using excipients that prolong the contact time of topically applied medicines. However, more effort must be made in this area to develop

Copyright © 2003 Marcel Dekker, Inc.

formulations/devices/processes that result in an increase in the levels of active ingredients that poorly penetrate into internal tissues. In addition, more selectivity (i.e., targeted delivery to specific regions of the eye) would be an advantage to prolong activity and to decrease the irritation that is sometimes induced by a bolus dose.

II. CHALLENGES IN DEVELOPING AN OPHTHALMIC DRUG DELIVERY SYSTEM

A. Anatomical and Physiological Features of the Eye

The eye (Fig. 1) is a unique organ for drug delivery. Many excellent reviews can be found in the literature that describe the anatomical and physiological features of the eye, written from the perspective of drug delivery [2–8].

Many of these anatomical and physiological features interfere with the fate of the administered drug. First and foremost are blinking, tear secretion, and nasolacrimal drainage. Lid closure upon reflex blinking protects the eye from external aggression. Tears permanently wash the surface of the eye and exert an anti-infectious activity by the lysozyme and immunoglobulins they contain. Eventually the lacrimal fluid is drained down the nasolacrimal pathways, then the pharynx and esophagus. This means that a portion of the drug is systematically delivered as if by the oral route. In addition, drug binding to tear proteins and to conjunctival mucin also inactivates a portion of the administered dose. Further

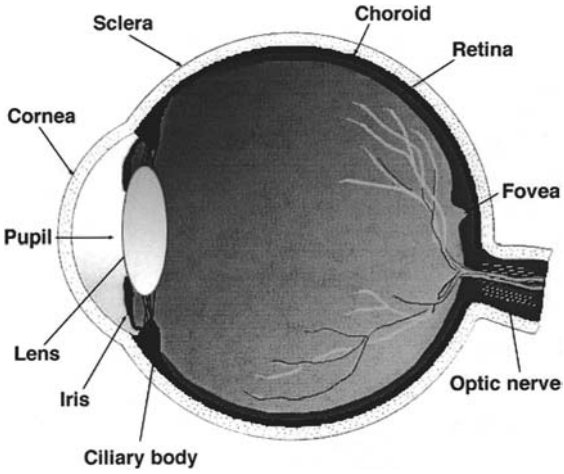


Figure 1 Cross section of the human eye.

Copyright © 2003 Marcel Dekker, Inc.

loss can arise through physical means. During administration, a part of an aqueous drop instilled in the patient's cul-de-sac is inevitably lost by overflow/drainage, since the conjunctival pouch can accommodate only approximately 20 μL of added fluid [9–11].

Precorneal losses are the Achilles heel of traditional aqueous formulations and the largest part of drug loss following ophthalmic administration occurs in front of the eye. It is no wonder that many researchers were attracted by the challenge to improve topical ophthalmic formulations.

Many attempts were made, but very few products actually completed a full development cycle and were made available for prescription.

B. Drug Delivery to the Internal Regions of the Eye

1. Eye Penetration of Drugs Administered Locally to the Eye

If the drug is not intended to act on the external surface of the eye, then the active ingredient has to enter the eye. There is consensus that the most important route is transcorneal; however, a noncorneal route has been proposed and may contribute significantly to ocular bioavailability of some ingredients, e.g., timolol and inulin [12]. In addition, the sclera has also been shown to have a high permeability for a series of β-blocking drugs [13].

Schematically, the cornea is a sandwich comprising a hydrophilic layer, the stroma, between two lipophilic layers, the epithelium and the endothelium (Fig. 2). The epithelium is composed of five to six layers of cells, whereas the endothelium is single-layered on the inner side of the cornea. In humans, the corneal thickness measures slightly more than 0.5 mm at the center and thickens a little at the periphery. The hydrophilic-lipophilic nature of the cornea clearly indicates that to be well absorbed, active ingredients have to exhibit to some extent both lipophilic and hydrophilic properties. For ionizable drugs, the pH of the formulation can be adjusted, within some limits, to favor transepithelial permeation of the un-ionized form. Pilocarpine, a natural alkaloid used in the treatment of glaucoma, has a pKa value of 7.15 [14], which is ideal for transcorneal penetration at physiological pH. However, as it hydrolyzes fairly rapidly at this pH, a weakly acidic buffer must be used in formulations of it.

Precorneal tear film produced by tear secretion keeps the cornea moist, clear, and healthy and is spread by the motion of eyelids during blinking. Drugs acting on tear secretion, physicochemical status of the tear film, and blinking can modify transcorneal drug permeation. Indeed, a major issue is the ratio of precorneal disappearance/transcorneal penetration. Robinson [15] calculated this ratio for pilocarpine and obtained a value of 100. In simple terms this means that a simple aqueous formulation is washed away from the precorneal area 100 times faster than this active ingredient penetrates the cornea.

Copyright © 2003 Marcel Dekker, Inc.

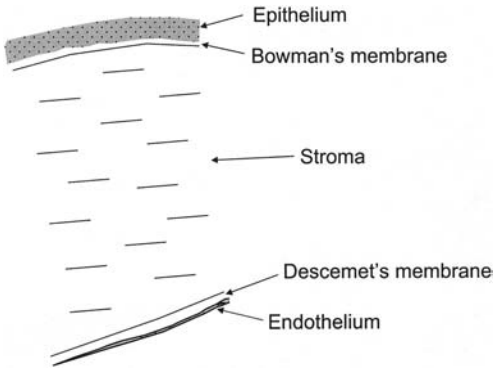


Figure 2 Schematic representation of the anatomy of the human cornea (electron microscopy). Central radius: 7.8 mm; overall thickness: 520 μm at center, approximately 670 μm at periphery; epithelium: five to six layers of cells, 50–60 μm thick; Bowman's layer: 8–12 μm thick; stroma: majority of the cornea essentially 200–250 layers of collagenous lamellae predominantly of type I collagen; Descemet's membrane: 8–12 μm thick; endothelium: simple squamous epithelium: 5–6-μm-high cells.

2. Eye Penetration of Systemically Administered Drugs

It is of interest to reflect on the eye penetration of systemically administered drugs, mostly anti-infectious and anti-inflammatory drugs. There are blood-eye barriers. Aqueous humor is produced by the ciliary epithelium in the ciliary processes. It is frequently named an ultrafiltrate, since the ciliary epithelium prevents the passage of large molecules, plasma proteins, and many antibiotics. Some molecules can be secreted in aqueous humor during its formation. Inflammation associated with injury, infection, or an ocular disease, e.g., uveitis, disrupts the blood–aqueous humor barrier and drugs enter the aqueous humor and reach the tissues of the anterior segment. There is a blood-retina barrier and there is one between blood and vitreous humor complicated by the high viscosity of the latter, which prevents diffusion of the drugs in the posterior part of the eye. Delivery of drugs to the posterior pole and to the retina is extremely difficult.

C. Assessment of the Performance of Ophthalmic Formulations

1. Pharmacokinetics

a. Rabbits Assessment of the performance of a modified-drug-release dosage form relies upon changes in bioavailability. When dealing with systemically administered dosage forms, kinetic studies of plasma levels are the basic tool to establish bioavailability. Needless to say, plasma levels are irrelevant to

Copyright © 2003 Marcel Dekker, Inc.

assess ocular bioavailability of topically administered ophthalmic drugs. However, assessment of the performance of a modified-release ophthalmic drug delivery system is based upon pharmacokinetic and/or pharmacodynamic studies.

There is a long history of invasive studies (e.g., aqueous humor levels) in animals, mainly in albino rabbits. This is because the rabbit is a very convenient animal in which to assess transcorneal penetration as a function of various factors such as salt, pH, adjuvants, etc. The rabbit and human eye do exhibit some similarities; the cornea is very similar in both species (but for the absence of Bowman's membrane in rabbits) and the aqueous humor composition is very similar in both species. However, essentially, rabbits and humans were not created equal in terms of eye physiology [16]. Rabbits blink only a few times per hour whereas humans blink 15–20 times per minute. Tear turnover is approximately 7% per minute in rabbits, compared to 16% in humans. The rabbit has a third eyelid—the nictitating membrane. This structure does not exist in humans. Also, the drainage rate constant is approximately 0.545/min in rabbits and three times larger, approximately 1.545/min in humans. In general, therefore, the respective precorneal parameters between rabbit and human are dissimilar. This means that formulations modified to change their behavior in the front of the cornea can act differently in the two species.

It is possible to obtain aqueous humor samples from patients undergoing cataract surgery, where the anterior chamber is open. This practice is not carried out very frequently and has serious ethical implications. However, it provides a unique opportunity to compare aqueous humor levels obtained in humans versus those obtained in rabbits. It is interesting to note that data published for the drug dorzolamide tend to conclude that the transcorneal penetration is quite similar in the two species [17,18].

b. Humans Clearly, human studies that assess the performance of a modified-release ophthalmic drug delivery system rely essentially on noninvasive methods.

Precorneal disposition can be studied using tear sampling and measurement of tear levels of the drug(s). It should be noted, however, that such a procedure can induce excessive blinking and tear production in subjects sensitive to the sampling pipette, and therefore induce a bias in the results. Moreover, when dealing with formulations that do not mix rapidly with tear film, one can sample a small piece of the formulation itself, thus making the assay results from such a sample meaningless.

There is another way to appreciate the disappearance of the drug in front of the eye, i.e., spiking the formulation or its vehicle with surrogate markers that can be easily measured. Essentially, these markers are fluorescent or radioactive entities and numerous data on precorneal disposition have been generated using these techniques [19–23].

Ultimately one can think that a specific property of a molecule, of a group

Copyright © 2003 Marcel Dekker, Inc.

of atoms, or of an atomic constituent of the molecule can be used, e.g., ^{18}F atom in imirestat [24] and Raman spectrum properties of dorzolamide [25]. These procedures are not yet used in humans to the best of our knowledge.

2. Pharmacodynamics

Drug pharmacodynamics are used when pharmacokinetic properties cannot be [26]. Some biological responses, such as miosis, mydriasis, intraocular pressure, and bactericidal activity, are easy to assess quantitatively, whereas the appreciation of leakage from the retinal vessels is by far more difficult. It is mandatory when using pharmacological activity as a measurement of changes in bioavailability not to overlook the need to be in the linear part of the dose-response curve. Otherwise, even with a change in C_{max}, the response will plateau and nothing can be deduced from the experiment [27].

D. Excipients

Finally, yet importantly, ophthalmic drug delivery systems are more demanding than oral formulations in terms of constituents. The external tissues of the eye's cornea and conjunctivae are very easily damaged by chemicals. This is why the controversial Draize test [28,29], which can assess minor aggressions to living tissues, is performed in rabbit eyes. Since the eye is so exquisitely sensitive to irritation, active ingredients and excipients of a modified-release ophthalmic drug delivery system must be very well tolerated. The formulator is usually rather conservative when selecting the constituents of the final formula of an ophthalmic product. Based on common sense and scrutiny from the regulatory agencies, only excipients with a known history of good tolerance are used. If a product that has never been formerly used in an ophthalmic product provides the solution to a critical issue in formulating, all information on its safety and previous human use, including use in food and/or cosmetics, has to be compiled and an ocular tolerance study must be performed. The International Pharmaceutical Excipient Council (IPEC) published a proposal for guidelines to extend the use of excipients formerly approved for a different route [30].

E. Other Formulation Considerations

Among other constraints, the ophthalmic formulation must be sterile. The preferred sterilization process is autoclaving—sometimes irradiation, followed by final sterile filtration, and finally, aseptic manufacturing. Unfortunately, many polymers do not withstand autoclaving or irradiation and their viscosity precludes the use of sterile filtration. *In fine*, multidose ophthalmic formulations must con-

Copyright © 2003 Marcel Dekker, Inc.

tain an antimicrobial preservative in compliance with the current pharmacopoeias and regulations.

The criteria for antimicrobial effectiveness are such that very few compounds can be used and many formulations rely on benzalkonium chloride or similar quaternary ammonium compounds. However, anionic molecules can interact with quaternary ammoniums and approximately 5% of patients are prone to develop intolerance toward them. Nonpreserved formulations may be administered from a unit dose.

III. FORMULATION APPROACHES

The preceding summary demonstrated that the formulator faces many constraints and prerequisites when developing a modified-release topical ophthalmic drug. In addition to the traditional requirements of oral drugs for safety, efficacy, and stability, ophthalmic products must exhibit additional properties. These are listed in Table 1.

An appreciation of the formulation approaches taken for the eye can be gained when one consults the reviews that are periodically published on ophthalmic drug delivery [31–40].

Table 1 Qualities of a Modified-Release Ophthalmic Drug Delivery System

A well-designed modified release ophthalmic drug delivery system must:
Deliver the active ingredient to the right place, i.e., high conjunctival levels are useless when targeting the ciliary body.
Improve the ratio of local activity versus systemic effects.
Reduce the number of installations per day, once-a-day being considered the optimal goal, although some can consider twice daily is a better insurance against a forgotten administration.
Be easy to self-administer.
Not induce a foreign-body sensation, long-lasting blurring, or a very bad aftertaste.
Not rely on “exotic” ingredients like new chemical entities or difficult-to-source excipients (unless this is a key element). Preferably, excipients should have a drug master file and history of safe use for humans.
Be sterilizable at industrial scale by a recognized process.
Be compatible with an efficient antimicrobial preservative, or packaging in unit doses must be a viable alternative.
Preferably be stored without specific conditions.
Be covered by a patent, since manufacturers can legitimately expect a return on R&D investment.

Copyright © 2003 Marcel Dekker, Inc.

The regulatory demands for new ophthalmic chemical entities are, most of the time, outweighed by the development efforts and costs compared to the size of the ophthalmic market. Indeed, because of the small size of the ophthalmic market, it is rather unrealistic to think that manufacturers would develop a totally new chemical entity specifically for ophthalmic use since the return on investment—if any—would be very slow. However, some derivatives have appeared in recent times, e.g., timolol base hemihydrate instead of timolol maleate [41–43]. Therefore, in terms of developing a modified-release ophthalmic drug delivery system, the formulator usually attempts to modify the formulation to optimize the release and delivery of an existing drug [31–40]. Primary approaches attempt to slow down the elimination of the active ingredient drained by the tear flow [44–46].

A. Viscous Solutions and Hydrogels

Viscous solutions and hydrogels, based upon the addition of hydrocolloids to simpler aqueous solutions, are the most common formulations. There is no clear-cut frontier between very viscous solutions and gels in terms of biopharmaceutical results. However, preformed gels are administered in the same way as an ointment, which is less convenient for the patient than the instillation of a viscous drop. The most common polymers used in viscous solutions are cellulose derivatives, carbomers, polysaccharides, and, recently, hyaluronic acid. The advantage offered by this last product could be dependent upon the active ingredient and the formulation environment [47]. Polyvinyl alcohol and polyvinyl pyrolidone are also used in ophthalmic drugs.

Gels permit longer residence time in the precorneal area than viscous solutions. This has encouraged researchers to work on formulations that would be (viscous) solutions in the drug vials but would gel in the conjunctival cul-de-sac. Three main mechanisms were explored to induce the sol/gel transition in the conjunctival pouch, namely a change in pH, a change in temperature, or a change in ionic environment [48–50]. Eventually one formulation of timolol, which was based on gellan gum that underwent a sol/gel transition due to the ionic content of the tears, reached the market in 1994 (Timoptic XE™) [50,51].

B. Dispersed Systems

Dispersed systems based on liposomes, nanoparticles, or nanocapsules have been extensively studied for potential ophthalmic use [52–56]. The development of marketable products based on these nanoproducts has been very challenging and a definitive technology has not yet been established. The major issues for this type of delivery system include: percentage of dispersed phase/entrapment coefficient problem (i.e., how much of the active ingredient will be present in a drop of the

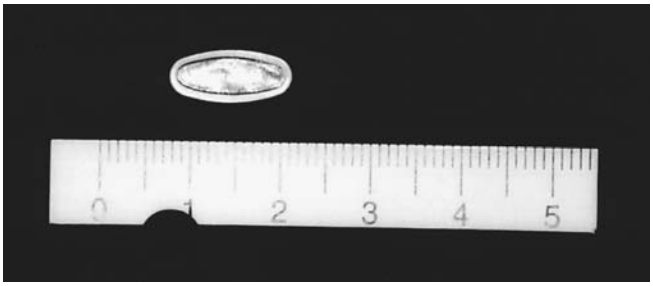
Copyright © 2003 Marcel Dekker, Inc.

final product), stability and shelf life, antimicrobial preservation, tolerance of the used surfactants, and, last but not least, large-scale manufacture of sterile preparations.

C. Inserts

Ophthalmic inserts have been, and continue to be, in fashion in research and development laboratories, which is testified to by an abundance of literature [57–59].

The insert is probably the oldest ophthalmic formulation. Such preparations are reported to have been used by the Gallo-Romans early in the Christian era. However, although the British Pharmacopoeia 1948 described an atropine in gela-



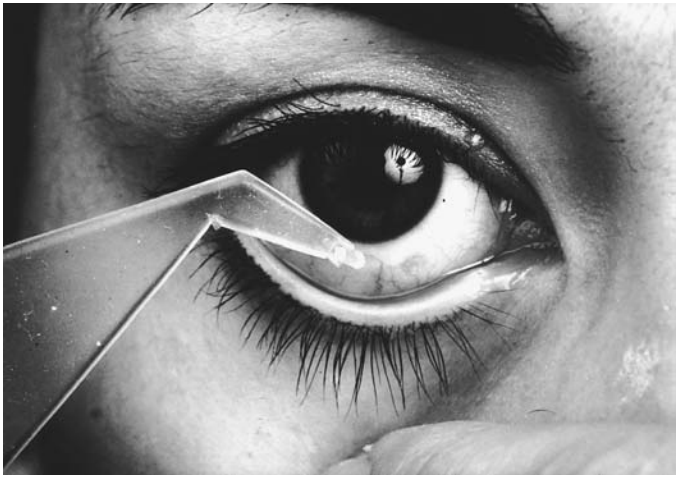
(A)

(B)

Figure 3 (A) Alza Ocusert. (B) Alza Ocusert in the conjunctival sac.

Copyright © 2003 Marcel Dekker, Inc.

(A)



(B)

Figure 4 (A) Merck & Co Lacrisert and its soft applicator. (B) Merck & Co Lacrisert ready for placing in the conjunctival sac.

Copyright © 2003 Marcel Dekker, Inc.

tin "wafer," and notwithstanding all the formulation possibilities as well as the modulation of biopharmaceutical properties that inserts permit, the insert market never took off. This was apparently caused by incompatibility between the product-insert and the user-patient, particularly in the elderly; difficulty of insertion by the patient, foreign-body sensation, and ultimately loss of inserts are reasons that are commonly reported. However, many additional factors might predict a pharmaceutical success [60]. A few physicians have casually expressed the opinion that the increasing use of soft contact lenses by patients will accustom and train them to place solid items close to their cornea and will reverse this situation.

Two products, Alza Ocusert® (Fig. 3) [61] and Merck Lacrisert® (Fig. 4) [62], have been marketed, although Ocusert is no longer sold. Ocusert was an insoluble delicate sandwich technology filled with sufficient pilocarpine for 1 week's use, whereas Lacrisert is a soluble minirod of hydroxypropyl cellulose, nonmedicated and dissolving within 24 h to treat dry-eye syndromes [62].

Other inserts are more like implants to be placed in the eye tissues by surgery and are not within the present scope of this review.

IV. RECENT RESEARCH

Clearly, the quest is challenging for the development of ophthalmic formulations that deliver effective ocular drug concentrations for an extended period (without inducing systemic side effects), that are user friendly, and that do not induce blurring, burning, or foreign-body sensation. Many attempts have been made to develop practical approaches to the modified delivery of drugs to the eye. Some have been described above. These are still being actively pursued today (except for the insoluble insert Ocusert). However, the ophthalmic area is a very active area of drug delivery research and many new technologies have been researched in recent times, some of which are described below.

Although patient complaints have been the major obstacle to the success of ophthalmic inserts, the field of veterinary medicine is still open to these formulations [63]. A soluble bioadhesive ophthalmic drug insert (BODI®) was recently described and is presently marketed for veterinary use in Europe [64,65].

Gelfoam® is made of absorbable gelatin sponge USP. It can be inserted in the conjunctival pouch in the form of small disks (e.g., 4 mm in diameter and 0.5 mm thick) impregnated with drug solutions. They have been shown to improve the management of pupillary dilation in humans as well as the delivery of pilocarpine [66–68].

NODS (Novel Ocular Delivery System) is essentially an "insert with a handle" [69,70] and will be fully discussed in a later chapter.

Collagen shields have been extensively described [71]. They appeared useful as a delivery system for anti-infective agents and might possibly be of interest

Copyright © 2003 Marcel Dekker, Inc.

for some other drugs. However, their size and the constraints they impose on vision render them impractical for a new drug delivery system. Suspensions of collagen microparticulates (e.g., Collasomes or Lacrisomes) might be better accepted [72].

In situ forming gels have been actively pursued. Product(s) using the gellan gum technology [73], and with polymer associations like those published by the University of Nebraska researchers [74,75], and Smart Gel® technology [76] are examples of technologies that use this approach. This field of intricately entangled polymers seems promising since new "patentable" entities might be obtained through in-depth studies of associations of well-established products. The aqueous formulations of such mixtures exhibit changes in physical properties, i.e., sol → gel transformation, with changes in the environment, e.g., temperature, pH, or ionic strength.

Chitosan is emerging as a polymer of interest for ophthalmic use [77–79].

Formulations based on the concept of mucoadhesion have been investigated to overcome the rapid elimination of instilled ophthalmic solutions. They appear less viscous than those based on traditional viscolizers. A number of polymers with polar/ionized groups have been selected and tested with ophthalmic drugs. In theory, prolonged retention of ophthalmic mucoadhesive formulations is due to electrostatic interactions that occur at the negatively charged corneal surface with the charged groups of the mucoadhesive. This theory has been explored since the end of the 1980s and recent reviews essentially describe experimental results [81–86]. At present no ophthalmic formulation is marketed that claims to rely on a bioadhesive excipient as the foundation of its release properties. Durasite® (polycarbophil) is progressing as a potential ophthalmic vehicle in this respect [87].

Products have recently emerged for use in the diagnostic field and as medicated intraocular implants [88–90]. Vitrasert® is an intravitreal implant approved by the FDA, which can release ganciclovir over a 5–8-month period. After depletion of the active ingredient, the implant may be removed and replaced [91]. Other intraocular formulations of ganciclovir have been developed [92,93]. Surodex, a biodegradable polymer based intraocular insert, is presently developed for postcataract surgery inflammation [94,95]. A viscous poly (orthoester) vehicle containing dexamethasone sodium phosphate and 5-fluorouracil, tested in subconjunctival injection in rabbits, might be of interest to control wound healing after filtering surgery [96,97]. Intraocular polysulfone fibers have been mentioned [98] as well as liposomes in a gel formulation [99].

Ion exchange resins have been investigated and resulted in the technology used in the product Betoptic S™ to improve bioavailability and to decrease irritation.

The potential of microparticulate formulations has been described but, as

Copyright © 2003 Marcel Dekker, Inc.

of today, they are not frequently employed as part of ophthalmic vehicles [100–103].

Nanosized systems based on liposomes, nanoparticles, and nanocapsules have been extensively studied and published and call the ophthalmic formulator's attention. Beyond the problem of the entrapment percentage of the active pharmaceutical ingredient, the retention of these particles in the conjunctival pouch is a key consideration. This retention must be effective in providing an extended source of active and to allow the drug to leak out from the dispersed phase before the instilled formulation is drained away from the precorneal area. Positively charged liposomes were described to have a greater affinity for ocular tissues [80]. A possible vehicle to administer these delicate nanosystems could be a gel, as was described for liposomes [104,105]. The industrial technology to produce sterile dispersed nanosystems has yet to be firmly established.

Microemulsions might be systems of future interest, with the basic caveats concerning sterile manufacturing, long-term stability, patient tolerance vis-à-vis any surfactant, and the difficulty to adequately preserve a biphasic system. Pilocarpine was described to largely benefit from such a formulation, and cyclosporine is a potential candidate for it [106–117].

Cyclodextrin-based formulations should not be missed by ophthalmic drug development groups [118,119]. Their typical domain of use would be sparingly soluble drugs, e.g., sulfonamides inhibiting carbonic anhydrase for the treatment of glaucoma [120] or steroids against inflammation [121,122]. However, their action might be equivocal: a cyclodextrin solution of L 671,152 (dorzolamide hydrochloride, a topically active sulfonamide) induced—in rabbits—intraocular levels lower than the corresponding suspension [123].

Since the instilled volume of vehicle is a factor of loss and because the use of small instilled volumes/high concentrations of drug is not deemed practical, volatile ophthalmic vehicles have been explored, as well as the concept of dry drops. A dry-drop formulation was declared not to be statistically different from a conventional solution [124]. It should be reminded that an "ophthalmic rod" without any liquid vehicle was described at the end of the seventies [125].

Perfluoro carbon vehicles were patented [126,127] and it was published that perfluorodecalin was tested in healthy human volunteers [128]. This compound was generally well tolerated and the retention of charcoal particulates led the investigators to forecast a potential for the perfluorodecalin system for the treatment of periocular diseases.

Sprays are again under consideration [129] although Mitsura®—a pilocarpine spray—was not a success in the mid-seventies. Sprays might, however, be useful in pediatric medicine [130].

The claim stating that some agents such as surfactants and preservatives [131–133] could be used as penetration promoters or enhancers was not con-

Copyright © 2003 Marcel Dekker, Inc.

firmed by actual formulation development, which is not bad since they can be locally toxic to the eye.

Prodrugs have been periodically proposed as the solution to solve ocular penetration and kinetics problems. However, since they could be considered as new chemical entities by many regulatory agencies, they have never become an established approach. A review of the literature reveals that there have been no new compounds since dipivefrin [134], although latanoprost (Xalatan®) was designed as a prodrug. For reviews on the use of prodrugs in ophthalmology refer to references 135 and 136.

An examination of the topical ophthalmic medicines clearly indicates that they are targeted at diseases of the anterior segment of the eye. The posterior pole is the poor cousin in terms of dedicated drugs and effective therapies [137]. In some countries, nonsteroidal anti-inflammatory agents are administered to prevent the cystoid macular edema consecutive to cataract surgery (for such drugs refer to ref. 138). Dorzolamide, a topically effective carbonic anhydrase inhibitor, has been described to have positive effects on retinal arteriovenous passage time of fluorescein [139], although it has been reported that sulfonamides do not reach the retina in therapeutic amounts after topical administration [140]. This opinion has been challenged [141].

Iontophoresis periodically reappears as a technique that could greatly improve intraocular levels of many ophthalmic active ingredients [142,143] and might be the technique to deliver antivirals, steroids, peptides, and nucleotides into the eye [144–147]. Recent progress in the technology of the associated hardware has stimulated interest in a renewal of its use in ophthalmology.

The use of lectins as mucosal bioadhesins in body cavities, e.g., in the conjunctival pouch, has been advocated [148]. The irritancy of lectins from *Solanum tuberosum* (potato) and from *Helix pomatia* (snail) has been studied, and was found to be minimal [149]. The authors declared they would investigate them further for use in ocular formulations [149].

A Boston team used an osmotic micropump to obtain transcleral delivery of bioactive proteins in pigmented rabbit eyes [150]. The anti-intercellular adhesion molecule-1 (ICAM-1) monoclonal antibody inhibiting vascular endothelial growth factor (VEGF) was successfully delivered to the choroid while levels in other eye tissues and plasma were found to be extremely low. This last point has been a recurring concern for all drugs from the ophthalmic formulators' viewpoint [151]. Osmotic micropumps have also been subconjunctivally implanted by a Purdue University team for continuous ocular treatment in horses [152]. Veterinary ophthalmology can certainly benefit from progress in ocular drug delivery [153].

The posterior segment of the eye is a matter of growing concern due to retinal diseases linked to the increasing size of the elderly population. Biomaterials used in this part of the eye have been reviewed and future directions received

Copyright © 2003 Marcel Dekker, Inc.

consideration in a recent paper [154]. The antiangiogenic agent TNP-470 was conjugated with poly (vinyl) alcohol at the University of Kyoto and tested in rabbits against experimental choroidal neovascularization (CNV). It was concluded that the targeted delivery of TNP-470-PVA might have potential as a treatment modality of CNV [155]. Thapsigargin-coated intraocular lenses placed postsurgery in the lens capsule prevented human lens cell growth. Thapsigargin is an endoplasmic reticulum Ca^{2+} ATPase inhibitor. It allows postsurgical opacification of the posterior capsule to be avoided [156].

Bleomycin, an antiproliferative antibiotic, has been delivered by electric pulses to the eyes of pigmented rabbits that underwent trabeculectomy as in glaucoma surgery. The treated group exhibited a significantly lower intraocular pressure (IOP) for up to 40 days after surgery [157]. The potential of gene therapy in ocular inflammation was reviewed by Nussenblatt and Csaky [158]. Two papers were published on the development of rabbit conjunctival and corneal cell cultures to study drug transport [159,160]. Since an improved knowledge of intraocular levels would tremendously assist in designing ophthalmic delivery systems, new analytical tools can greatly benefit this process. Microdialysis techniques were studied in this respect and it was concluded they could be of critical interest to facilitate construction of ocular pharmacokinetic/pharmacodynamic relationships [161].

Last, but not least, the photodynamic therapy applied for the treatment of age-related macular degeneration provides an example of the controlled endocular activity of a systemically administered drug (verteporfin, Visudyne®). The drug, a photosensitizer, is systematically administered and occurs at higher concentrations in the neovessels. A specific laser beam is targeted to the neovessel foci and induces the formation of chemicals triggering the coagulation cascade. Such a treatment stops the progression of the disease for several months [163].

V. CONCLUSIONS

The above review of the modes of administering medicines to a sore eye testifies to the fascination that the treatment of ocular diseases has exerted on scientists. Obviously the boundaries are expanding as far as optimization of drug delivery to the eye is concerned [162]. Some of the technologies discussed above are more fully described in other chapters, which shed light on the different needs for modified-release ophthalmic formulations. The development of the ionic suspension of betaxolol deals with the need to reduce irritancy induced by the active ingredient and with the tuning of the sustained-release properties. The research and development process resulted in a 0.25% suspension exhibiting the therapeutic activity of a 0.50% solution. The NODS chapter describes a solution to a basic problem inherent to ocular inserts, the insertion of the device into the pa-

Copyright © 2003 Marcel Dekker, Inc.

tient's eye. It also describes some of the difficulties one can encounter with respect to technology development and regulatory compliance. Finally, the BODI chapter describes a solution to a lesser-known problem, the treatment of ocular infections in animals. The chapter demonstrates that the use of erodible inserts can deliver anti-infectious active ingredients for longer periods than drops, thereby decreasing the need for handling animals.

It is difficult, and probably vain, to forecast the ophthalmic dosage forms of the future but, whatever the future, even when the active ophthalmic ingredients are identified, the development path to a marketable ophthalmic product will not be easy. Pharmaceutical research and development provides a pathway to achieve this, but it is governed by available technology, innovations in technology, and regulatory constraints. Importantly, the cost of the finished product must be bearable by the individuals and/or communities who will use the product, and it has to be economically viable for the manufacturer. As a final thought, it must be kept in mind that the most exquisite modified-release technology for an established drug can be made obsolete by the arrival of a new drug; the pilocarpine Ocusert© technology began to decline with the introduction of beta-blocking drugs to ophthalmic medicine.

When all the factors that are described in this chapter are combined, they make the area of ophthalmic drug delivery a very exciting challenge.

ACKNOWLEDGMENTS

The invaluable assistance of Ms. Marjorie Cremont and of Ms. Sylviane Rousselin for revising and handling the electronic manuscript is gratefully acknowledged.

REFERENCES

1. Ophthalmic Drug Facts. St. Louis, MO: Facts and Comparisons. A Wolters Kluwer Company, 2000.
2. JS Cumming. Relevant anatomy and physiology of the eye. In: JR Robinson. ed. Ophthalmic Drug Delivery Systems. Washington, DC: American Pharmaceutical Association, 1980, pp. 1–27.
3. JL Greaves. Ocular drug delivery. In: CG Wilson, N Washington, eds. Physiological Pharmaceutics: Biological Barriers to Drug Absorption. Chichester: Ellis Horwood Ltd., 1989, pp. 121–138.
4. JC Robinson. Ocular anatomy and physiology relevant to ocular drug delivery. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 29–57.

Copyright © 2003 Marcel Dekker, Inc.

5. J Stjernschantz, M Astin. Physiological aspects of ocular drug therapy. In: P Edman, ed. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL CRC Press, 1993, pp. 1–25.
6. SS Chrai, TF Patton, A Mehta, JR Robinson. Lacrimal and instilled fluid dynamics in rabbit eye. J Pharm Sci 62:1112–1121, 1973.
7. A Ludwig, M Van Ooteghem. The influence of the drop size on the elimination of an ophthalmic solution from the precorneal area of human eyes. Pharm Acta Helv 62:56–60, 1987.
8. MM Van Ooteghem. Factors influencing the retention of ophthalmic solutions on the eye surface. In: MF Saettone, G Bucci, P Speiser, eds. Ophthalmic Drug Delivery: Biopharmaceutical, Technological and Clinical Aspects. Fidia Research Series, Vol. 11, Padova, Italia: Liviana Press, 1987, pp. 7–17.
9. WL White, AT Glover, AB Buckner. Effect of blinking on tear elimination as evaluated by dacryoscintigraphy. Ophthalmology 98:367–369, 1991.
10. VHL Lee. Precorneal, corneal and postcorneal factors. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 59–81.
11. NEML Tang, PL Zuure, RD Pardo, RJW de Keizer, JA Van Best. Reflex lacrimation in patients with glaucoma and healthy control subjects by fluorophotometry. Invest Ophthalmol Vis Sci 41:709–714, 2000.
12. I Ahmed, TF Patton. Importance of non corneal absorption route in topical ophthalmic drug delivery. Invest Ophthalmol Vis Sci 26:584–587, 1985.
13. RD Schoenwald, GS Deshpande, DG Rethwisch, CF Barfknecht. Penetration into the anterior chamber via the conjunctival/scleral pathway. J Ocul Pharmacol Ther 13:41–59, 1997.
14. Pilocarpine (monograph Nr 7578). In: SB Budavari, ed. The Merck Index. 12th ed. Whitehouse Station, NJ: Merck & Co, 1996, pp. 1277.
15. JR Robinson. Ocular drug delivery mechanism(s) of corneal drug transport and mucoadhesive delivery systems. STP Pharma Sci 5:839–846, 1989.
16. D Maurice. The effect of the low blink rate in rabbits on topical drug penetration. J Ocul Pharmacol Ther 11:297–303, 1995.
17. MF Sugrue. The preclinical pharmacology of dorzolamide hydrochloride, a topical carbonic anhydrase inhibitor. J Ocul Pharmacol Ther 12:363–376, 1996.
18. K Schmitz, P Banditt, M Motschmann, FP Meyer, W Bebrens-Baumann. Population pharmacokinetics of 2% topical dorzolamide in the aqueous humor of humans. Invest Ophthalmol Vis Sci 40:1621–1624, 1999.
19. A Ludwig, M Van Ooteghem. The study of the precorneal dynamics of ophthalmic solutions by fluorophotometry. Pharm Acta Helv 61:236–240, 1986.
20. CG Wilson. Scintigraphic evaluation of polymeric formulations for ophthalmic use. In: MF Saettone, G Bucci, P Speiser, eds. Ophthalmic Drug Delivery: Biopharmaceutical, Technological and Clinical Aspects. Fidia Research Series, Vol. 11. Padova, Italia: Liviana Press, 1987, pp. 141–150.
21. JL Greaves, CG Wilson, A Rozier, J Grove, B Plazonnet. Scintigraphic assessment of an ophthalmic gelling vehicle in man and rabbit. Curr Eye Res 9:415–420, 1990.
22. G Meseguer, R Gurny, P Buri, A Rozier, B Plazonnet. Gamma scintigraphic study of precorneal drainage and assessment of miotic response in rabbits of various ophthalmic formulations containing pilocarpine. Int J Pharm 95:229–234, 1993.

Copyright © 2003 Marcel Dekker, Inc.

23. G Meseguer, P Buri, B Plazonnet, A Rozier, R Gurny. Gamma scintigraphic comparison of eyedrops containing pilocarpine in healthy volunteers. J Ocul Pharmacol Ther 12:481–488, 1996.
24. G Vaidyanathan, M Jay, RK Bera, PR Mayer, RK Brazzell. Scintigraphic evaluation of the ocular disposition of ^{18}F-imirestat in rabbits. Pharm Res 7:1198–1200, 1990.
25. NJC Bauer, M Motamedi, JP Wicksted, WF March, CAB Webers, F Hendrikse. Non-invasive assessment of ocular pharmacokinetics using confocal Raman spectroscopy. J Ocul Pharmacol Ther 15:123–134, 1999.
26. DDS Tang-Liu, A Acheampong, DS Chien, JI Usansky. Pharmacokinetics and pharmacodynamic correlations of ophthalmic drugs. In: J Reddy, ed. Ocular Therapeutics and Drug Delivery: A Multiplisciplinary Approach. Lancaster, PA: I-Technomic Publishing Co., 1996, pp. 133–147.
27. B Plazonnet. Ophthalmics. In: Bioequivalence of special dosage forms. Kurz nr 442 APV symposium. Berlin, April 3, 2000. Arbeitsgemeinschaft für Pharmaceutische Verfahrenstechnik e.v., Kurfurstenstrasse 59-D55118, Mainz.
28. JH Draize, G Woodard, HO Calvery. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 82:377–390, 1944.
29. FDA Illustrated Guide for Grading Eye Irritation by Hazardous Substances. Washington, DC: Government Printing Office, 1965.
30. IPEC Europe Safety Committee. The proposed guidelines for the safety evaluation of new excipients. Eur Pharm Rev 2:13–20, 1997.
31. JR Robinson, ed. Ophthalmic Drug Delivery Systems. Washington, DC: American Pharmaceutical Association, 1980.
32. VHL Lee, JR Robinson. Review: Topical drug delivery: recent developments and future challenges. J Ocul Pharmacol 2:67–108, 1986.
33. MF Saettone, G Bucci, P Speiser, eds. Ophthalmic Drugs Delivery: Biopharmaceutical, Technological, Clinical Aspects. Fidia Research Series, Vol. 11. Padova, Italia: Liviana Press, 1987.
34. VHL Lee. Review: New directions in the optimization of ocular drug delivery. J Ocul Pharmacol 6:157–164, 1990.
35. P Edman. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993.
36. AK Mithra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993.
37. M Van Ooteghem, ed. Préparations Ophtalmiques, Paris: Technique & Documentation, 1995.
38. JP Frangie. Clinical pharmacokinetics of various topical ophthalmic delivery systems. Clin Pharmacokin 29:130–138, 1995.
39. C Le Bourlais, L Acar, H Zia, PA Sado, T Needham, R Leverge. Ophthalmic drug delivery systems—recent advances. Prog Ret Eye Res 17:33–58, 1998.
40. S Ding. Recent developments in ophthalmic drug delivery. Pharm Sci Technol Today 8:328–335, 1998.
41. WC Stewart. Timolol hemihydrate: a new formulation of timolol for the treatment of glaucoma. J Ocul Pharmacol Ther 12:225–236, 1996.

Copyright © 2003 Marcel Dekker, Inc.

42. WC Stewart, TM Leland, EA Cate, JA Stewart. Efficacy and safety of timolol solution once daily vs. timolol gel in treating elevated IOP. J Glaucoma 7:402–407, 1998.
43. WC Stewart, EA Cate, JA Stewart. Systemic β-blockade with once daily Betimol or Timoptic-XE. J Ocul Pharmacol Ther 15:225–231, 1999.
44. O Olejnik. Conventional systems in ophthalmic drug delivery systems. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker. 1993, pp. 177–198.
45. M Van Ooteghem. Collyres. Guttae ophthalmicae. In: M Van Ootegehem, ed. Préparations Ophtalmiques. Paris: Technique & Documentation-Lavoisier, 1995, pp. 58–100.
46. P Buri, F Gurtler. Les formes ophtalmiques à action prolongée. In: M Van Ooteghem, ed. Préparations Ophtalmiques. Paris: Technique & Documentation-Lavoisier, 1995, pp. 127–215.
47. SF Bernatchez, O Camber, C Tabatabay, R Gurny. Use of hyaluronic acid. In: P Edman, ed. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993, pp. 105–120.
48. R Gurny, H Ibrahim, P Buri. The development and use of in situ formed gels, triggered by pH. In: P Edman, ed. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993, pp. 81–90.
49. GO Waring, RR Harris. Double-masked evaluation of a poloxamer artificial tear in keratoconjunctivitis sicca. In: IH Leopold, RP Burns, eds. Symposium on Ocular Therapy. Vol. 11. New York: John Wiley & Sons, 1993, pp. 127–140.
50. A Rozier, C Mazuel, J Grove, B Plazonnet. Gelrite: a novel, ion activated, in-situ gelling polymer for ophthalmic vehicles: effect on bioavailability of timolol. Int J Pharm 57:163–168, 1989.
51. R Vogel, SF Kulaga, JK Laurence, RL Gross, BG Haik, D Karp, M Koby, TJ Zimmerman. The effect of a Gelrite vehicle on the efficacy of low concentration of timolol. Invest Ophthalmol Vis Sci 31:404, 1990 [ARVO Mtg Abstract # 1990].
52. R Gurny, T Boye, H Ibrahim. Ocular therapy with nanoparticulate systems for controlled drug delivery. J Control Rel 2:353–361, 1985.
53. VHL Lee, PT Urrea, RE Smith, DJ Schauzun. Ocular drug bioavailability from topically applied liposomes. Surv Ophthalmol 29:335–348, 1985.
54. L Marchal-Heussler, D Sirbat, M Hoffman, P Maincent. Poly (ε-caprolactone) nanocapsules in carteolol ophthalmic delivery. Pharm Res 10:386–390, 1993.
55. M Mezei, D Meisner. Liposomes and nanoparticles as ocular drug delivery systems. In: P Edman, ed. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993, pp. 91–104.
56. NM Davies, JL Greaves, IW Kellaway, CG Wilson. Advanced corneal delivery systems: liposomes. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 289–306.
57. YF Maichuk. Ophthalmic drug inserts. Invest Ophthalmol 14:87–90, 1975.
58. MF Seattone. Solid polymeric inserts/disks as drug delivery devices. In: P Edman, ed. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993, pp. 61–79.

Copyright © 2003 Marcel Dekker, Inc.

59. SW Friedrich, BA Saville, Y-L Cheng, DS Rootman. Pharmacokinetic differences between ocular inserts and eyedrops. J Ocul Pharmacol Ther 12:5–18, 1996.
60. S Bawa. Ocular inserts. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 223–260.
61. J Urquhart. Development of Ocusert pilocarpine ocular therapeutic systems. In: JR Robinson, ed. Ophthalmic Drug Delivery Systems. Washington, DC: American Pharmaceutical Association, 1980, pp. 105–108.
62. Merck & Co. US patent 4,343,787, 1982.
63. PI Punch, DH Slatter, ND Costa, M Edwards. Ocular inserts for application of drug to bovine eyes—in vitro studies of gentamicin release from collagen inserts. Aust Vet J 69:79–82, 1985.
64. F Gurtler, V Kaltsatos, B Boisrame, J Deleforge, M Gex-Fabry, R Balant, R Gurny. Ocular availability of gentamicin in small animals after topical administration of a conventional eye drop solution and a novel long acting bioadhesive ophthalmic drug insert. Pharm Res 12:1791–1795, 1995.
65. V Bayens, V Kaltsatos, B Boisrame, M Fathi, R Gurny. Evaluation of soluble bioadhesive ophthalmic drug inserts (BODI) for prolonged release of gentamicin: lachrymal pharmacokinetics and ocular tolerance. J Ocul Pharmacol Ther 14:263–272, 1998.
66. P Simamora, SR Nadkarni, YC Lee, SH Yalkowshy. Controlled delivery of pilocarpine. 2. In-vivo evaluation of Gelfoam device. Int J Pharm 170:209–214, 1998.
67. YC Lee, JW Millard, GJ Negvesky, SI Butrus, SH Yalkowsky. Formulation and in vivo evaluation of ocular insert containing phenylephrine and tropicamide. Int J Pharm 182:121–126, 1999.
68. GJ Negvesky, SI Butrus, HA Abifarah, YC Lee, SH Yalkowsky. Ocular Gelfoam disc-applicator for pupillary dilation in humans. J Ocul Pharmacol Ther 16:311–315, 2000.
69. MC Richardson, PH Bentley. A new ophthalmic delivery system. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 355–367.
70. M Diestelhorst, GK Krieglstein. The ocular tolerability of a new ophthalmic drug delivery system (NODS). Int Ophthalmol 18:1–4, 1994.
71. JM Hill, RJ O'Callaghan, JA Hobden, HE Kaufman. Corneal collagen shields for ocular delivery. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 261–273.
72. HE Kaufman, TL Steinemann, E Lehman, HW Thompson, ED Varnell, JT Jacob-Labarre, BM Gebhardt. Collagen-based drug delivery and artificial tears. J Ocul Pharmacol 10:17–27, 1994.
73. Merck & Co. US patent 4,861,760, 1989.
74. S Kumar, BO Haglund, KJ Himmelstein. In situ–forming gels for ophthalmic drug delivery. J Ocul Pharmacol 10:47–56, 1994.
75. S Kumar, KJ Himmelstein. Modification of in situ gelling behavior of carbopol solutions by hydroxypropyl methylcellulose. J Pharm Sci 84:344–348, 1995.
76. ES Ron. Smart Gel: A new thermogelling polymer mixture for drug delivery. Proc Int Symp Control Rel Bioact Mater 23:23–24, 1996.

Copyright © 2003 Marcel Dekker, Inc.

77. O Felt, P Buri, R Gurny. Chitosan: a unique polysaccharide for drug delivery. Drug Dev Ind Pharm 24:979–993, 1998.
78. O Felt, P Furrer, JM Mayer, B Plazonnet, P Buri, R Gurny. Topical use of chitosan in ophthalmology: tolerance assessment and evaluation of precorneal retention. Int J Pharm 180:185–193, 1999.
79. O Felt, A Carrel, P Baehni, P Buri, R Gurny. Chitosan as tear substitute: a wetting agent endowed with antimicrobial efficacy. J Ocul Pharmacol Ther 16:261–270, 2000.
80. HE Schaeffer, DL Krohn. Liposomes in topical drug delivery. Invest Ophthal Vis Sci 22:220–227, 1982.
81. JM Gu, JR Robinson, SHS Leung. Binding of acrylic polymers to mucin/epithelial surfaces: structures-property relationships. Crit Rev Ther Drug Carr Syst 5:21–67, 1988.
82. NM Davies, SJ Farr, J Hadgraft, IW Kellaway. Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions. Pharm Res 8:1039–1043, 1991.
83. EM Slovin, JR Robinson. Bioadhesives in ocular drug delivery. In: P Edman, ed. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993, pp. 145–157.
84. R Krishmamoorthy, AK Mitra. Mucoadhesive polymers in ocular drug delivery. In: AK Mitra, ed. Ophthamic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 199–221.
85. MF Saettone, D Monti, MT Torracca, P Chetoni. Mucoadhesive ophthalmic vehicles: evaluation of polymeric low-viscosity formulations. J Ocul Pharmacol 10:83–92, 1994.
86. F Thermes, J Grove, G Chastaing, A Rozier, K Soper, B Plazonnet. Effects of a mucolytic agent, acetylcysteine, on bioadhesion and ocular penetration. STP Pharma Sci 2:88–92, 1992.
87. R Patel. US patent 5,340,572, 1994.
88. JA Schulman, GA Peyman. Intracameral, intravitreal and retinal drug delivery. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 383–425.
89. DC Metrikin, R Anand. Intravitreal drug administration with depot devices. Curr Opin Ophthalmol 5:21–29, 1994.
90. P Ashton, DL Blandford, PA Pearson, GJ Jaffe, DF Martin, RB Nussenblatt. Review: Implants. J Ocul Pharmacol 10:691–701, 1994.
91. Ganciclovir intravitreal implant (Vitrasert). In: Ophthalmic Drug Facts. St. Louis, MO: Facts and Comparisons. A Wolters Kluwer Co., 2000, pp. 150–153.
92. P Ashton, JD Brown, PA Pearson, DL Blandfor, TJ Smith, R Anand, SD Nightingale, GE Sanborn. Intravitreal ganciclovir pharmacokinetics in rabbits and man. J Ocul Pharmacol 8:343–347, 1992.
93. T Yasukawa, H Kimura, N Kunou, H Miyamoto, Y Honda, Y Ogura, Y Ikada. Biodegradable scleral implant for intravitreal controlled release of ganciclovir. Graefes Arch Clin Exp Ophthalmol 238:186–190, 2000.
94. DT Tan, SP Chee, L Lim, AS Lim. Randomized clinical trial of a new dexamethasone delivery system (Surodex) for treatment of post-cataract surgery inflammation. Ophthalmology 106:223–231, 1999.

Copyright © 2003 Marcel Dekker, Inc.

95. DF Chang, V Wong. Two clinical trials of an intraocular steroid delivery system for cataract surgery. Trans Am Ophthalmol Soc 97:261–274, 1999.
96. S Einmahl, M Zignani, E Varesio, J Heller, JL Veuthey, C Tabatabay, R Gurny. Concomitant and controlled release of dexamethasone and 5-fluorouracil from poly(ortho ester). Int J Pharm 185:189–198, 1999.
97. M Zignani, E Einmahl, V Baeyens, E Varesio, JL Veuthey, J Anderson, J Heller, C Tabatbay, R Gurny. A poly(ortho ester) designed for combined ocular delivery of dexamethasone sodium phosphate and 5-fluorouracil: subconjunctival tolerance and in vitro release. Eur J Pharm Biopharm 50:251–255, 2000.
98. MH Rahimy, GA Peyman, SY Chin, R Golshani, C Aras, H Borhani, H Thompson. Polysulfone capillary fiber for intraocular drug delivery: in vitro and in vivo evaluations. J Drug Target 2:289–298, 1994.
99. A Bochot, P Couvreur, E Fattal. Intravitreal administration of antisense oligonucleotides: potential of liposomal delivery. Prog Ret Eye Res 19:131–147, 2000.
100. R Jain, O Gan, Y Ali, R Rodstrom, S Hancock. Ion exchange resins for ophthalmic delivery. J Ocul Pharmacol 10:57–67, 1994.
101. A Joshi. Microparticulates for ophthalmic drug delivery. J Ocul Pharmacol 10:29–45, 1994.
102. AM Durrani, SJ Farr, JW Kellaway. Precorneal clearance of mucoadhesive microspheres from the rabbit eye. J Pharm Pharmacol 47:581–584, 1995.
103. I Genta, B Conti, P Perugini, F Pavanetto, A Spadaro, G Puglisi. Bioadhesive microspheres for ophthalmic administration of acyclovir. J Pharm Pharmacol 49:337–342, 1997.
104. A Bochot, E Fattal, JL Grossiord, F Puisieux, P Couvreur. Characterization of a new ocular delivery system based on a dispersion of liposomes in a thermosensitive gel. Int J Pharm 162:119–127, 1998.
105. A Bochot, E Fattal, A Gulik, G Couarraze, P Couvreur. Liposomes dispersed within a thermosensitive gel: a new dosage form for ocular delivery of oligonucleotides. Pharm Res 15:1364–1369, 1998.
106. M Nakano. Place of emulsions in drug delivery. Adv Drug Del Rev 45:1–4, 2000.
107. MJ Lawrence, GD Ress. Microemulsion-based media as novel drug delivery systems. Adv Drug Del Rev 45:89–121, 2000.
108. T Cohen, H Sauvageon-Martre, D Brossard, F D'Hermies, C Bardin, F Chast, JC Chaumeil. Amphotericin B eye drops as a lipidic emulsion. Int J Pharm 137:249–254, 1996.
109. U Ticho, M Blumenthal, S Zonis, I Blank, Z Maror. Piloplex, a new long-acting pilocarpine polymer salt. A. Long term study. Br J Ophthalmol 63:45–47, 1979.
110. U Ticho, Z Maror, L Rose. Piloplex, a new long acting pilocarpine polymer salt B: comparative study of the visual effects of pilocarpine and Piloplex eyedrops. Br J Ophthalmol 65:48–51, 1979.
111. M Sznitowska, K Zurowska-Pryczkowska, S Janicki, T Järvinen. Miotic effect and irritation potential of pilocarpine prodrug incorporated into a submicron emulsion vehicle. Int J Pharm 184:115–120, 1999.
112. N Naveh, S Muchtar, S Benita. Pilocarpine incorporated into a submicron emulsion vehicle causes an unexpectedly prolonged ocular hypotensive effect in rabbits. J Ocul Pharmacol 10:509–520, 1994.

Copyright © 2003 Marcel Dekker, Inc.

113. A Acheampong, M Shackleton, S Lam, P Rudewiez, D Tang-Liu. Cyclosporine distribution into the conjuctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes. Adv Exp Med Biol 438:1001–1004, 1998.
114. A Acheampong, M Shackleton, D Tang-Liu, S Ding, M Stern, R Decker. Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs. Curr Eye Res 18:91–203, 1999.
115. D Stevenson, J Tauber, BL Reis. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose ranging, randomized trial: the cyclosporin A phase 2 study group. Ophthalmology 107:967–974, 2000.
116. BA Klyashchitzky, AJ Owen. Drug delivery systems for cyclosporine: achievements and complications. J Drug Target 5:443–458, 1998.
117. O Angelov, A Wiese, Y Yuan, J Anderson, A Acheampong, B Brar. Preclinical safety studies of cyclosporine ophthalmic emulsion. Adv Exp Med Biol 438:991–995, 1998.
118. T Loftssona, T Jarvinen. Cyclodextrins in ophthalmic drug delivery. Adv Drug Del Rev 1:59–79, 1999.
119. DC Bibby, NM Davies, IG Tucker. Mechanisms by which cyclodextrins modify drug release from polymeric drug delivery systems. Int J Pharm 197:1–11, 2000.
120. E Guomundstottir, E Stefansson, G Bjarnadottir, JF Sigurjonsdottir, G Guomunsdottir, M Masson, T Loftsson. Methazolamide 1% in cyclodextrin solution lowers IOP in human ocular hypertension. Invest Ophthalmol Vis Sci 41:3552–3554, 2000.
121. JK Kristinsson, H Fridriksdottir, S Thorisdottir, AM Sigurdardottier, E Stefansson, T Loftsson. Dexamethasone-cyclodextrin-polymer co-complexes in aqueous eye drops. Aqueous humor pharmacokinetics in humans. Invest Ophthalmol Vis Sci 37:1199–1203, 1996.
122. NM Davies, G Wang, IG Tucker. Evaluation of a hydrocortisone/hydroxypropyl-β-cyclextrin solution for ocular drug delivery. Int J Pharm 156:201–209, 1997.
123. J Grove, MP Quint, B Plazonnet. Influence of β-cyclodextrin on intraocular penetration of the topical carbonic anhydrase inhibitor, L-671-152 in rabbits. Poster presented at 5th International Symposium on Cyclodextrins, Paris, March 28–30, 1990.
124. M Diestelhorst, S Grunthal, R Suverkrup. Dry drops: a new preservative-free drug delivery system. Graefes Arch Clin Exp Ophthalmol 237:394–398, 1999.
125. SD Alain. The ophthalmic rod: description of a disposable ophthalmic drug delivery device. Acta Pharm. Suec 15:237–240, 1978.
126. DL Meadows. US patent 5,173,298, 1992.
127. DL Meadows. US patent 5,518,731, 1996.
128. Y Zhu, CG Wilson, D Meadows, O Olejnik, M Frier, N Washington, R Musson. Dry powder dosing in liquid vehicles: ocular tolerance and scintigraphic evaluation of a perfluorocarbon suspension. Int J Pharm 191:79–85, 1999.
129. EA Doe, JA Campagna. Pilocarpine spray: an alternative delivery method. J Ocul Pharmacol Ther 14:1–4, 1998.

Copyright © 2003 Marcel Dekker, Inc.

130. JO Benavides, ER Satchell, KA Frantz. Efficacy of a mydriatic spray in the pediatric population. Optom Vis Sci 74:160–163, 1997.
131. J Liaw, JR Robinson, Penetration enhancers. In: AK Mitra, ed. Ophthamic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 369–381.
132. H Sasaki, T Nagano, K Yamamura, K Nishida, J Nakamura. Ophthalmic preservatives as absorption promoters for ocular drug delivery. J Pharm Pharmacol 47:703–707, 1995.
133. H Sasaki, K Yamamura, T Mukai, J Nakamura, M Nakashima, M Idrikawa. Enhancement of ocular drug penetration. Crit Rev Ther Drug Carr Syst 16:85–146, 1999.
134. C Wer, JA Anderson, I Leopold. Ocular absorption and metabolism of topically applied epinephrine and a dipivalyl ester of epinephrine. Invest Ophthalmol Vis Sci 17:315–321, 1978.
135. VHL Lee. Improved ocular drug delivery by use of chemical modification (prodrugs). In: P Edman, ed. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993, pp. 121–143.
136. N Bodor. Recent advances in retrometabolic design approaches. J Control Rel 62: 209–222, 1999.
137. DH Geroski, HF Edelhauser. Drug delivery for posterior segment eye disease. Invest Ophthalmol Vis Sci 41:961–964, 2000.
138. Nonsteroidal anti-inflammatory agents (NSAIDS). In: Ophthalmic Drug Facts. St. Louis, MO: Facts and Comparisons. A Wolters Kluwer Company, 2000, pp. 88–92.
139. A Harris, O Arend, L Kagemann, M Garrett, HS Chung, B Martin. Dorzolamide, visual function and ocular hemodynamics in normal-tension glaucoma. J Ocul Pharmacol Ther 15:189–197, 1999.
140. CW Conroy. Sulfonamides do not reach the retina in therapeutic amounts after topical application to the cornea. J Ocul Pharmacol Ther 13:465–472, 1997.
141. MF Sugrue. Pharmacology and ocular hypotensive properties of topical carbonic anhydrase inhibitors. Prog Ret Eye Res 19:87–112, 2000.
142. JM Hill, RJ O'Callaghan, JA Hobden. Ocular iontophoresis. In: AK Mitra, ed. Ophthamic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 331–354.
143. D. Sarraf, DA Lee. The role of iontophoresis in ocular drug delivery. J Ocul Pharmacol 10:69–81, 1994.
144. TT Lam, J Fu, R Chu, K Stojack, E Siew, MOM Tso. Intravitreal delivery of ganciclovir by transscleral iontophoresis. J Ocul Pharmacol 10:571–575, 1994.
145. FF Behar-Cohen, JM Parel, Y Pouliquen, B Thillaye-Goldenberg, O Goureau, S Heydolph, Y Courtois, Y De Kozak. Iontophoresis of dexamethasone in the treatment of endotoxin-induced-uveitis in rats. Exp Eye Res 65:533–545, 1997.
146. J Frucht-Pery, D Goren, A Solomon, CS Siganos, H Mechoulam, A Solomon, P Ever-Hadani, M Shapiro. The distribution of gentamicin in the rabbit cornea following iontophoresis to the central cornea. J Ocul Pharmacol Ther 15:251–256, 1999.
147. T Asahara, K Shinomiya, T Naito, H Shiota. [Introduction of genes into the rabbit eye by iontophoresis]. Nippon Ganka Gakka Zasshi 103:178–185, 1999 [in Japanese].

Copyright © 2003 Marcel Dekker, Inc.

148. MA Clark, BH Hirst, MA Jepson. Lectin-mediated mucosal delivery of drugs and microparticles. Adv Drug Del Rev 43:207–223, 2000.
149. JD Smart, TJ Nichols, KL Green, DJ Rogers, JD Cook. Lectins in drug delivery: a study of the acute irritancy of the lectins from *Solanum tuberosum* and *Helix pomatia*. Eur J Pharm Sci 9:93–98, 1999.
150. J Ambati, ES Gragoudas, JW Miller, TT You, K Miyamoto, FC Delori, AP Adamis. Transscleral delivery of bioactive protein to the choroid and retina. Invest Ophthalmol Vis Sci 41:1186–1191, 2000.
151. A Urtti, L Salminen. Minimizing systemic absorption of topically administered ophthalmic drugs. Surv Ophthalmol 37:443–456, 1993.
152. MJ Blair, JR Gionfriddo, LM Polazzi, JE Sojka, AM Pfaff, DP Bingaman. Subconjunctivally implanted micro-osmotic pumps for continuous ocular treatment in horses. Am J Vet Res 60:1102–1105, 1999.
153. R Gurny, R Kaltsatos, AA Deshpande, M Zignani, C Percicot, V Baeyens. Ocular drug delivery in veterinary medicine. Adv Drug Del Rev 28:335–361, 1997.
154. MJ Colthurst, RL Williams, PS Hiscott, I Grierson. Biomaterials used in the posterior segment of the eye. Biomaterials 21:649–665, 2000.
155. T Yasukawa, H Kimura, Y Tabata, H Miyamoto, Y Honda, Y Ikada, Y Ogura. Targeted delivery of anti-angiogenic agent TNP-470 using water soluble polymer in the treatment of choroidal neovascularization. Invest Ophthalmol Vis Sci 40: 2690–2696, 1999.
156. G Duncan, IM Wormstone, CS Liu, JM Marcantonio, PD Davies. Thapsigargin-coated intraocular lenses inhibit human lens cell growth. Nat Med 3:1026–1028, 1997.
157. Y Oshima, T Sakamoto, T Nakamura, Y Tahara, Y Goto, T Ishibashi, H Inomata. The comparative benefits of glaucoma filtering surgery with an electric-pulse targeted drug delivery system demonstrated in an animal model. Ophthalmology 106: 1140–1146, 1999.
158. RB Nussenblatt, K Csaky. Perspectives on gene therapy in the treatment of ocular inflammation. Eye 11:217–221, 1997.
159. JJ Yang, H Ueda, K Kim, VH Lee. Meeting future challenges in topical ocular drug delivery: development of an air-interfaced primary culture of rabbit conjunctival epithelial cells on a permeable support for drug transport studies. J Control Rel 65: 1–11, 2000.
160. VR Goskonda, RA Hill, MA Khan, IK Reddy. Permeability of chemical delivery systems across rabbit corneal (SIRC) cell line and isolated corneas: a comparative study. Pharm Dev Technol 5:409–416, 2000.
161. KD Rittenhouse, GM Pollack. Microdialysis and drug delivery to the eye. Adv Drug Del Rev 45:229–241, 2000.
162. JC Keister, ER Cooper, PJ Missel, JC Lang, DF Hager. Limits on optimizing drug delivery. J Pharm Sci 80:50–53, 1991.
163. NM Bressler, SB Bressler. Photodynamic therapy with verteporfin (Visudyne): impact on ophthalmology and visual sciences. Invest Ophthalmol Vis Sci 41:624–628, 2000.

Copyright © 2003 Marcel Dekker, Inc.

26

Ion Exchange Resin Technology for Ophthalmic Applications

Rajni Jani and Erin Rhone
Alcon Research Ltd., Fort Worth, Texas, U.S.A.

I. INTRODUCTION

Only a few commercially available ophthalmic drug delivery systems have been forthcoming since the introduction of the topical eyedrop. However, delivery systems that attempt to increase the residence time in the eye have been extensively studied in the literature. Among these are presoaked soft contact lenses [1–7], soluble polymer gels [8,9] and emulsions [10–12], bioerodible ocular inserts [13], diffusional devices or nonerodible inserts [14], and osmotic systems [15]. Of these delivery systems, the Ocusert® system (Alza Corporation, Palo Alto, CA), which was introduced in 1975, provided a virtual zero-order release of the drug over a long period of time. Although it was technologically advanced, the Ocusert system was not well accepted by patients.

For a patient with a chronic ocular disease such as glaucoma, efficient drug delivery can make the difference between long-term well-being and morbidity of the patient. The conventional method for treating this condition is by the use of eyedrops. This approach results in an initial peak dose of drug, which is usually higher than that needed for therapeutic effect, followed by a dropoff in concentration below therapeutic levels [15]. This fluctuating therapeutic course is exacerbated when the patient is reluctant to take the medication because of systemic or localized side effects. The ion exchange resin technology is a means by which this disease can be treated more effectively with the fluctuating drug levels being controlled through formulation.

Copyright © 2003 Marcel Dekker, Inc.

II. ION EXCHANGE RESIN TECHNOLOGY

A. History

The introduction of a topical ophthalmic betaxolol 0.5% solution (Betoptic® Solution 0.5%) in 1985 offered a breakthrough for patients with compromised cardiac and pulmonary function. The beta-1-adrenergic cardioselectivity of betaxolol hydrochloride was proven effective in lowering intraocular pressure with fewer side effects than either timolol maleate or levobunolol. However, the introduction of betaxolol ionic suspension (Betoptic S) in 1990 provided an even more significant innovation because it provided the same efficacy as betaxolol solution but with a superior safety and tolerance profile.

B. Product Challenges

The development of topical ophthalmic dosage forms of a nonselective beta-1- and beta-2-adrenergic antagonist provided ophthalmologists with two powerful tools for the treatment of open-angle glaucoma and elevated intraocular pressure. However, although beta blockers are effective in lowering and maintaining normal intraocular pressure, they are also known to have the potential for significant systemic side effects and local irritation.

1. Systemic Side Effects

Since the majority of glaucoma patients are over 60 years of age and susceptible to age-related body changes (i.e., cardiac and pulmonary function), systemic absorption of any drug following ocular administration must be evaluated carefully to avoid drug toxicity and to avoid exacerbating systemic side effects.

2. Local Irritation

In addition to systemic side effects, the beta-blockers used in glaucoma topical therapy are known to produce a brief episode of stinging and/or burning upon instillation in some patients. The discomfort associated with topical administration of betaxolol 0.5% solution is due to the high localized concentration of drug at the cornea nerve endings. Betaxolol is a lipophilic molecule, which resembles a long hydrophobic chain with a small hydrophilic end-group. Because of this hydrophobicity, it penetrates the cornea very well. Since the cornea has a network of sensory nerve endings making it very sensitive to external stimuli, exceeding the threshold value causes the nerve ending to fire, resulting in discomfort. Thus to improve comfort (or reduce discomfort) it is necessary to reduce and/or control the penetration of betaxolol into the cornea, thereby reducing the drug concentration below the threshold value at the nerve endings. This hypothetical threshold is shown in Figure 1.

Copyright © 2003 Marcel Dekker, Inc.

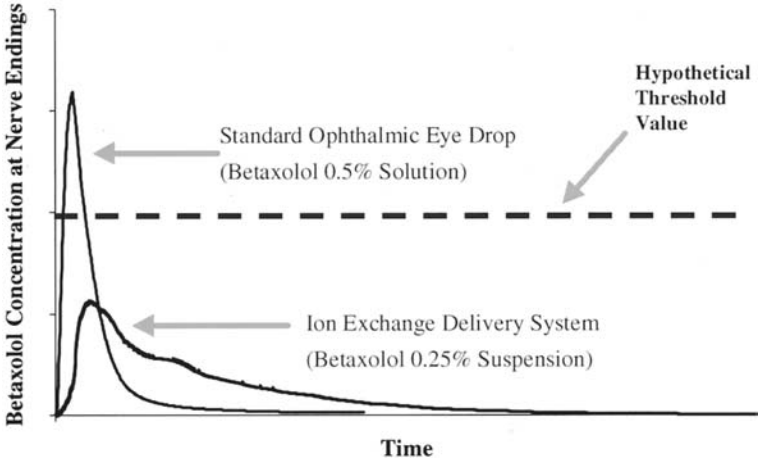


Figure 1 Hypothetical comfort threshold. (See color insert.)

C. Product Requirements

It was this side-effect profile that presented pharmaceutical scientists with the challenge of developing a delivery system that both minimized the ocular discomfort and reduced the systemic absorption that was associated with beta-blockers while maintaining efficacy.

In addition, ideally, the drug delivery system should also provide longer residence time in the precorneal area, and minimize systemic exposure thus providing the same amount (mass) of drug at one-half the concentration.

D. Ion Exchange Resins

The controlled release of a topical ophthalmic beta-blocker at a known release rate was achieved by binding betaxolol to an ion exchange resin.

1. History and Uses

Interest in the use of ion exchange resins as carriers for drug molecules began in the 1950s. Keating was one of the first to discuss the preparation and evaluation of combinations of carboxylic, sulfonic and phosphoric acid cation exchange resins with a variety of amine drugs (e.g., adrenergics, antihistaminics, antispasmodics, and antitussives) [16].

Ion exchange resins have been used to modify the release of drug molecules for systemic use for many years. Most major applications of resinate-type dosage

Copyright © 2003 Marcel Dekker, Inc.

forms have been for oral formulation. For example, Burke et al. used ion exchange resins for slow release of propranolol hydrochloride into the gastrointestinal tract [17]. Ion exchange resins have also been used as potential phosphate binders for renal failure patients.

The substance to which betaxolol is bound in the formulation is a pharmaceutical-grade cationic exchange resin, Amberlite™. Cationic exchange polymers have been used as carriers for cationic drugs in several pharmaceutical preparations, e.g., in numerous tablets (e.g., phentermine maleate), in cough syrups (e.g., Pennkinetic System), and to reduce problems of taste and odor in oral dosage forms. Amberlite ion exchange polymers have also been used in the controlled release of drugs.

2. Description of Ion Exchange Resins

Ion exchange resins are insoluble ionic materials with acidic or basic groups that are covalently bound in repeating positions on the resin chain. These charged groups associate with other ions of opposite charge. Depending on whether the mobile counterion is a cation or an anion, it is possible to distinguish between cationic and anionic exchange resins. The matrix in cationic exchangers carries ionic groups such as sulfonic carboxylate and phosphate groups. The matrix in anionic exchangers carries primary, secondary, tertiary, or quaternary ammonium groups. The resin matrix determines its physical properties, its behavior toward biological substances, and to some extent, its capacity.

III. ION EXCHANGE RESIN TECHNOLOGY FOR OPHTHALMIC APPLICATIONS

The first successful ophthalmic product for topical application using ion exchange resin technology was betaxolol ionic suspension (Betoptic S, 0.25%) for glaucoma, which was introduced by Alcon Laboratories in 1990 [18]. Alcon holds worldwide patents directed to sustained-release ophthalmic suspensions including Betoptic S.

A. The Formulation

Betaxolol ionic suspension contains 0.28% betaxolol hydrochloride equivalent to 0.25% betaxolol bound to Amberlite resin with 0.01% benzalkonium chloride as an antimicrobial preservative. The betaxolol ionic suspension formulation also contains disodium edetate, mannitol, hydrochloric acid, or sodium hydroxide to adjust the pH, and purified water as shown in Table 1.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Composition of Betoptic S

Ingredient	Concentration
Betaxolol hydrochloride	0.28%[a]
Mannitol	[b]
Disodium edetate	0.01%
Carbomer 934P	[b]
Amberlite[c]	[b]
Benzalkonium chloride	0.01%
Purified water	100.0%

[a] Equivalent to 0.25% betaxolol base.
[b] Proprietary data.
[c] The cationic exchange polymer is present in the formulation in sufficient quantity to bind 85% or more of the betaxolol present.

Chemically, betaxolol HCl is (+)-1[p-[2(cyclopropylmethoxy) ethyl]phenoxyl]-3-(isopropylamino)-2-propanol hydrochloride with empirical formula of $C_{18}H_{29}NO_3 \cdot HCl$ and a molecular weight of 343.89. Betaxolol HCl is a white crystalline powder, soluble in water with a melting point of 116°C. Betaxolol base is sparingly soluble in water with a melting point between 70° and 72°C. Figure 2 presents the chemical structure of betaxolol HCl.

Chemically, Amberlite resin is a styrene-vinyl copolymer. It is a sulfonic acid exchanger that has a negatively charged (SO_3^-) group that exists on the outer surface of the polymer to which the positively charged betaxolol molecule binds. The resin is the acid form of sodium polystyrene sulfonate, USP. The structure of the functional group is shown in Figure 3.

Manufacture of betaxolol ionic suspension involves dissolution of betaxolol and mannitol in purified water. Milled, acidified sodium polystyrene sulfonate resin is then dispersed into the betaxolol/mannitol solution. The carbomer-suspending agent is dispersed in purified water and added [19]. In this ultrafine

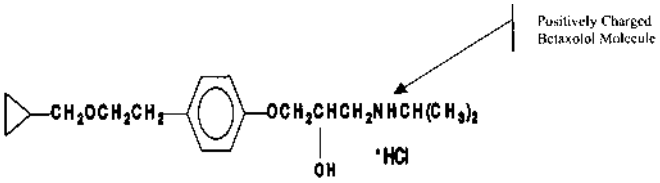


Figure 2 Betaxolol HCl.

Copyright © 2003 Marcel Dekker, Inc.

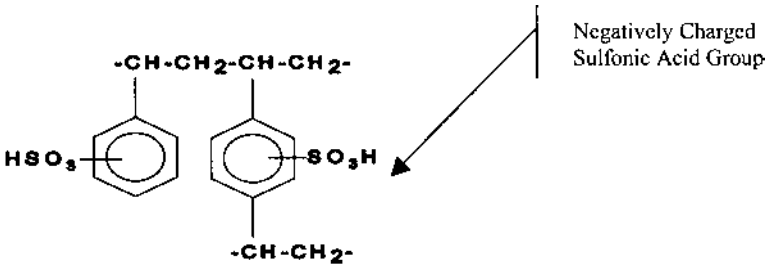


Figure 3 Amberlite resin [poly(styrenedivinylbenzene)sulfonic acid].

ophthalmic quality suspension, the ion exchange polymer is milled to a mean diameter, similar in size to steroid particles found in ophthalmic preparations. The particle size of the resin is readily controlled. Controlling and monitoring particle size of the resin employed in betaxolol ionic suspension has allowed for successful production of this product since 1990 in the United States. The manufacturer has established a stringent specification limit for betaxolol suspension of not less than 99.50% of particles <25 μm; not less than 99.95% of particles <50 μm; and not less than 100% of particles <90 μm.

Since the formulation contains a carbomer, sodium hydroxide is required to adjust to pH. The pH is targeted to be 7.0 to achieve acceptable bound betaxolol values. This pH value does not alter the comfort of the formulation.

Osmolality of the formulation is a fundamental consideration, which directly relates to ocular comfort. Sodium chloride and other ionic salts, which are frequently employed in formulations to adjust their osmolality, cannot be used in the betaxolol formulation since they would interfere with the betaxolol-resin binding. The nonionic compound mannitol was selected to render the formulation iso-osmotic since it is very soluble and has no effect on the binding of betaxolol to Amberlite resin [20].

In this ion exchange delivery system, positively charged betaxolol exists bound to the negatively charged sulfonic acid groups of the Amberlite resin. The extent of betaxolol binding to the resin in the formulation is directly proportional to the resin concentration. The cationic exchange resin of sulfonic acid polymers forms an ion exchange matrix suspended in a structural vehicle containing carbomer polymer. Since betaxolol HCl and the polymer are present in betaxolol ionic suspension in approximately equimolar ratios, conditions in the suspension allow about 85% of the betaxolol to be bound to the cation exchange polymer beads as shown in Figure 4.

Carbopol 934P is added to the formulation to increase its viscosity and therefore increase the residence time of the product in the eye. Carbopol polymer,

Copyright © 2003 Marcel Dekker, Inc.

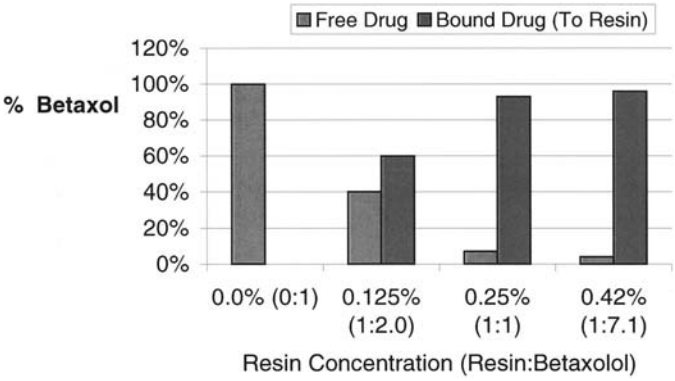


Figure 4 Betaxolol binding to resin. (See color insert.)

when hydrated, provides a network of polymer chains forming a structured vehicle in which particles stay suspended for a longer period [21]. These attributes are demonstrated by betaxolol ionic suspension's ability to provide uniform dosing of drug for up to 4 weeks without resuspending the product.

The physical properties of betaxolol ionic suspension distinguish it from other ophthalmic suspensions. Unique among these is the long period of time over which betaxolol ionic suspension remains suspended. To demonstrate this characteristic, eight bottles of betaxolol ionic suspension were resuspended at room temperature at time 0 (Fig. 5) and the betaxolol content was analyzed by high-performance liquid chromatography (HPLC) in duplicate samples. The remaining samples were left undisturbed. At weekly intervals, samples from two

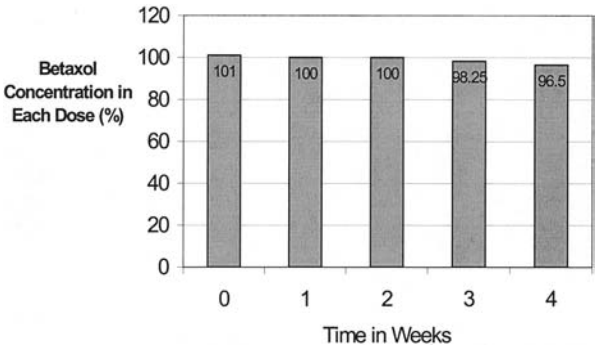


Figure 5 Settling time.

Copyright © 2003 Marcel Dekker, Inc.

bottles were dispensed without shaking or resuspension and the betaxolol assayed again by HPLC. As is apparent from Figure 5, the amount of betaxolol, expressed as a percent of label, is constant over the 4-week period. This demonstrated that betaxolol ionic suspension, once suspended, remained suspended over the duration of the study period. A further important characteristic of the suspension technology of betaxolol ionic suspension is that its excellent resuspendibility makes neither vigorous shaking nor shaking for long periods necessary. A few shakes with the wrist are adequate to resuspend betaxolol ionic suspension.

B. Patient Comfort

In the eye, as shown in Figure 6, betaxolol is readily released from the polymer, via exchange with positively charged ions like sodium, potassium, and calcium, which are natural constituents of tears. The net effect of placing one or two drops of betaxolol ionic suspension in the eye is that, as Na^+ is exchanged for betaxolol on the polymer, the beta-blocker is released relatively slowly into the lacrimal film. The kinetics of betaxolol release governs the neuronal responses in the eye (particularly those in the cornea) to the molecule. Since betaxolol is released into the lacrimal film more slowly from betaxolol ionic suspension than from betaxolol solution, patient comfort is enhanced.

Time-release profiles for two formulations of betaxolol 0.5% in two ophthalmic dosage forms, solution and suspension, were studied using a controlled-release analytical system (CRAS). CRAS is an in vitro technique for measuring time release profiles of ophthalmic dosage forms under conditions closely simulating those prevailing in the precorneal tear fluid [22]. The study found that the briefest profile resulted from simple solution. This resulted in rapid dumping, which represented the behavior expected for betaxolol 0.5% solution. Time re-

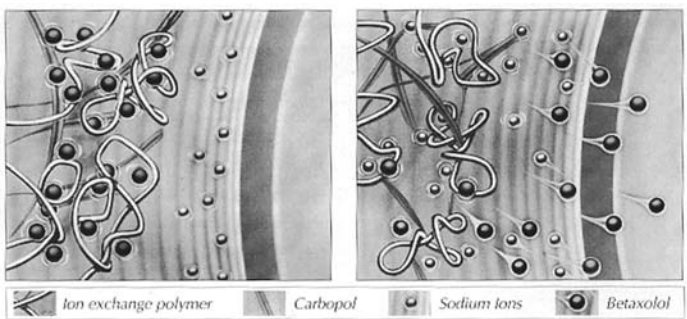


Figure 6 Mechanism of action of Betoptic Suspension eyedrop. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

lease for this preparation was essentially complete in 30 min. The use of an ion exchange resin in a simple 1:1 drug-to-resin ratio sustained drug release over a 2-h period and reduced the maximum drug concentration in the eluent (representing the precorneal tear fluid) to 30% compared to that of the solution.

These data suggested that sustained release formulations should reduce side effects, because the suspension will be retained within the cul-de-sac and drug released from the delivery system continuously (Fig. 7).

Glaucoma is a progressive disease, which puts the patient's visual prognosis at risk. To halt the progression of this neuropathological process, treatment should be taken for life. The prolonged daily application of eyedrops demands a high degree of patient compliance. The low potential for adverse events helps to maintain patient compliance. The degree of comfort of any treatment strongly influences patient compliance. To evaluate the degree of patient compliance, the tolerability of betaxolol suspension was studied in a number of clinical trials. In a 3-month double-masked, parallel-group clinical study, betaxolol ionic suspension 0.25% and betaxolol solution 0.5% were equally effective in reducing intraocular pressure [23]. An equally important conclusion drawn from this study was that statistically significantly fewer patients experienced stinging and burning during instillation of betaxolol ionic suspension, as shown in Figure 8. The greater ocular comfort of betaxolol ionic suspension was attributed to the lower drug concentration and because it was delivered slowly instead of in one bolus.

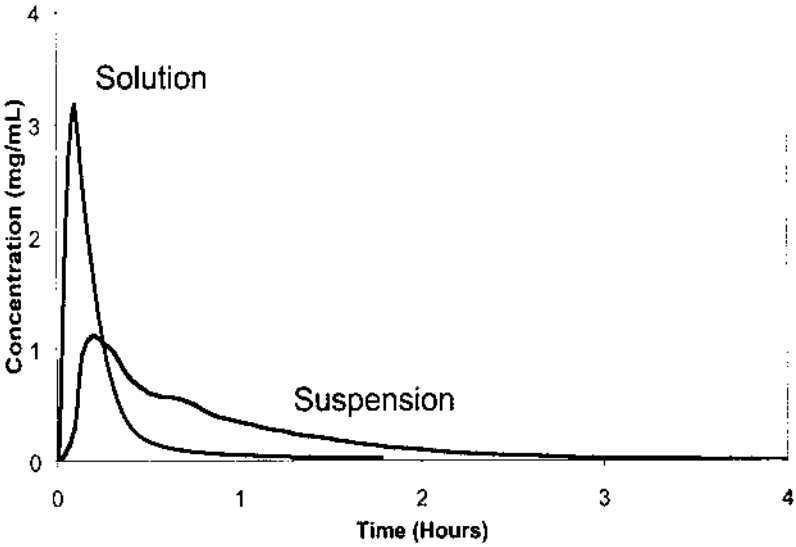


Figure 7 Comparison of time-release profiles from two preparations of betaxolol 0.5%.

Copyright © 2003 Marcel Dekker, Inc.

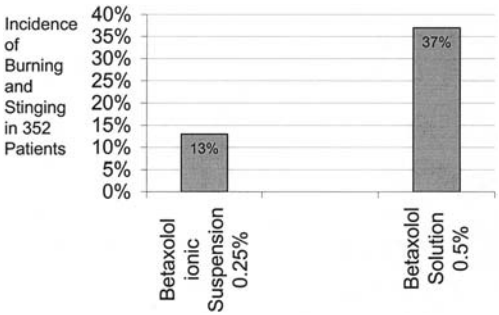


Figure 8 Comfort of Betoptic Suspension as compared to Betoptic Solution.

Finally, in a long-term study, data on the comfort of betaxolol ionic suspension showed that few patients reported stinging or burning on administration of the drops. These figures were lower than those reported in the 3-month controlled studies. The results indicated that the suspension did not become less comfortable with time [24].

C. Reduction of Systemic Side Effects

To conserve the physiological integrity of the body, local therapy for glaucoma treatment should not be absorbed into the systemic circulation and should be completely devoid of systemic side effects.

Glaucoma patients frequently present with hepatic and renal changes. This physiological deterioration affects the tolerability of a drug due to pharmacokinetic changes (including absorption, distribution, metabolism, and drug elimination). To obtain optimal tolerability in these individuals, the ion exchange technology when combined with the beta-1 selectivity of betaxolol resulted in a locally administered betaxolol that exhibited superior systemic tolerability to that of nonselective antiglaucomatous beta-blockers.

D. Dose Reduction

The ion exchange delivery vehicle that was developed allowed a twofold reduction in the concentration of topically administered betaxolol without an effect on the drug effectiveness. A study in animals demonstrated the ocular bioequivalence of betaxolol from Betoptic S and Betoptic Solution. The same study also showed the superior bioavailability of beta-blocker from betaxolol ionic suspension, compared to that of the 0.5% Betoptic Solution (see Fig. 9).

Copyright © 2003 Marcel Dekker, Inc.

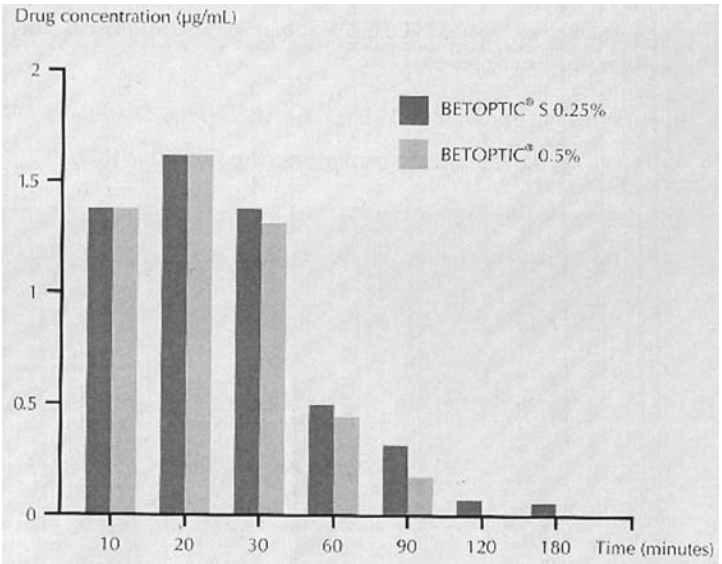


Figure 9 Betaxolol concentration in aqueous. (See color insert.)

E. Comparison with Conventional Ophthalmic Drops

As already discussed, the long period of time over which betaxolol ionic suspension remains suspended and the ease of resuspendibility of the betaxolol ionic suspension favorably differentiate it from other ophthalmic suspensions.

Betaxolol ionic suspension also differs from conventional suspension products, such as corticosteroid eyedrops, in that the delivery system was specifically designed to optimize bioavailability and patient comfort. The suspended exchange resin binds with betaxolol in the formulation and, upon instillation, gradually releases it to the eye, thus minimizing ocular discomfort associated with free betaxolol ions.

F. Regulatory Considerations

The original betaxolol ionic suspension was tested in accordance with the USP Preservative Efficacy Test (PET). However, to improve the preservative efficacy of the product beyond its ability to meet USP PET standards, an alternative formulation was developed to meet the more strenuous European Pharmacopoeia (Ph. Eur.) PET standards. The new formulation included boric acid and *N*-lauroylsarcosine.

Copyright © 2003 Marcel Dekker, Inc.

In addition to the new Ph. Eur. PET standards, a new Ph. Eur. Carbomer Monograph was adopted in 1999. To comply with the Ph. Eur. requirements eliminating benzene in carbomers, Carbopol 974P was substituted for Carbopol 934P. PET testing of betaxolol ionic suspension with boric acid and *N*-lauroyl-sarcosine as preservative aids and Carbopol 974P have shown that the changes in the formulation created a more robust preservative system.

G. In-Use Experience

Since the introduction of betaxolol solution in 1985, ophthalmologists have used betaxolol for the systemic safety advantages it offers. Although betaxolol ionic suspension was more easily tolerated than betaxolol solution, many ophthalmologists continued to prefer timolol maleate because of its efficacy advantages.

IV. RECENT DEVELOPMENTS

Researchers discovered that by changing the betaxolol molecule, they could make it more effective at lowering intraocular pressure. The result was levobetaxolol 0.5% (Betaxon). Levobetaxolol is an enantiomer of betaxolol. Animal work has indicated that the "levo" form of betaxolol—the S isomer—possesses greater activity than the dextro form. Betaxolol ionic suspension is composed of both the levo and dextro forms of betaxolol. These have been separated to formulate levobetaxolol ionic suspension, which contains only the levo form.

Since betaxolol and other beta-adrenergic antagonists have been shown to reduce intraocular pressure by a reduction of aqueous production, it is assumed that the mechanism of action of levobetaxolol ionic suspension is similar. Topical administration of levobetaxolol ionic suspension results in systemic exposure to levobetaxolol that is significantly less than that observed with topical dosing with betaxolol 0.5% solution. This suggests a reduced risk of adverse cardiovascular or respiratory events with levobetaxolol ionic suspension. It is thought that the low systemic exposure to levobetaxolol is due to the ion resin exchange suspension that releases the active drug slowly.

V. CONCLUSIONS

The ion exchange resin technology has been successfully combined with betaxolol and levobetaxolol to optimize the safety and efficacy of topically administered beta-blockers. For the drug betaxolol this drug delivery technology has resulted in a twofold increase in bioavailability without an associated increase in systemic absorption. In addition, the ion exchange resin technology has provided

Copyright © 2003 Marcel Dekker, Inc.

the first viable alternative to eyedrops by providing the controlled release of a high-performance therapeutic agent that is well tolerated by patients.

ACKNOWLEDGMENTS

To our colleagues in Pharmaceutics, Analytical Chemistry, ADME, Clinical Science, Microbiology, and Toxicology Departments of Alcon Research Ltd., Research and Development.

REFERENCES

1. HE Kaufman, AR Gasset. Therapeutic soft bandage lenses. Int Ophthalmol Clin 10: 379–385, 1970.
2. SR Waltman, HE Kaufman. Use of hydrophilic contact lenses to increase ocular penetration of topical drugs. Invest Ophthalmol 9:250–255, 1970.
3. HE Kaufman, MH Uotila, AR Gasset. The medical uses of soft contact lenses. Trans Am Acad Ophthalmol Otolaryngol 75:361–373, 1971.
4. JW Aquavella, GK Jackson, LF Guy. Therapeutic effects of bionite lenses: mechanisms of action. Ann Ophthalmol 3:1341–1345, 1971.
5. YT Maddox, HN Bernstein. An evaluation of bionite hydrophilic contact lens for use in a drug delivery system. Ann Ophthalmol 4:789–790, 1972.
6. SM Podos, B Becker, CF Asseff, J Harlstein. Pilocarpine therapy with soft contact lenses. Am J Ophthalmol 73:336–341, 1972.
7. CF Assef, RL Weisman, SM Podos. Ocular penetration of pilocarpine in primates. Am J Ophthalmol 75:212–215, 1973.
8. FE Leaders, G Hecht, M VanHoose, M Kellog. New polymers in drug delivery. Ann Ophthalmol 5:513–516, 1973.
9. AI Mandell, RM Stewart, MA Kass. Multiclinic evaluation of a pilocarpine gel. Invest Ophthalmol Vis Sci April (Suppl): 1979 (abstract).
10. U Ticho, M Blumenthal, S Zonis, A Gal, I Blank, ZW Mazor. A clinical trial with piloplex; a new long-acting pilocarpine compound: preliminary report. Ann Ophthalmol 11:555–561, 1979.
11. A Mazor, U Ticho, U Rehany, L Rose. Piloplex, a new long acting pilocarpine polymer salt. B. Comparative study of the visual effects of pilocarpine and piloplex eye drops. Br J Ophthalmol 63:48–51, 1979.
12. U Ticho, M Blumenthal, S Zonis, A Gal, I Blank, ZW Mazor. Piloplex, a new long acting pilocarpine polymer salt: a long term study. Br J Ophthalmol 63:45–47, 1979.
13. JW Shell, RW Baker. Diffusional systems for controlled release of drugs to the eye. Ann Ophthalmol 6:1037–1043, 1974.
14. S Lerman, P Davis, WB Jackson. Prolonged release hydrocortisone therapy. Can J Ophthalmol 8:114–118, 1973.
15. CH Dohlman, D Pavan-Langston, J Rose. A new ocular insert device for continuous constant-rate delivery of medication to the eye. Ann Ophthalmol 4:823–832, 1972.

Copyright © 2003 Marcel Dekker, Inc.

16. JW Keating. Pharmaceutical preparations comprising cation exchange resin absorption compounds and treatment therewith. US patent 2,990,332, 1961.
17. GM Burke, RW Mendes, SS Jambhekar. Investigation of the applicability of ion exchange resins as a sustained release drug delivery system for propranolol hydrochloride. Drug Dev Ind Pharm 12:713–721, 1986.
18. R Jani, R Harris. Sustained release, comfort formulations for glaucoma therapy. US patent 4,911,920, 1990.
19. Alcon unpublished data.
20. Alcon unpublished data.
21. BF Goodrich carbopol polymers product literature.
22. LE Stevens, PJ Missel, JC Lang. Drug release profiles of ophthalmic formulations. 1. Instrumentation. Anal Chem 64:715–723, 1992.
23. RN Weinreb, DR Caldwell, SM Goode, BL Horwitz, R Laibovitz, CE Shrader, SH Stewart, AT Williams. A double-masked three-month comparison between 0.25% betaxolol suspension and 0.5% betaxolol ophthalmic solution. Am J Ophthalmol 110:189–192, 1990.
24. Alcon unpublished data.

Copyright © 2003 Marcel Dekker, Inc.

27

New Ophthalmic Delivery System (NODS)

L. Sesha Rao
Chauvin Pharmaceuticals Ltd., Romford, Essex, England

I. INTRODUCTION

The new ophthalmic delivery system (NODS) is based on a presentation that was designed to deliver a finite amount of a drug or a diagnostic agent, contained within a water-soluble film, to the eye. This chapter outlines the underlying concepts, scientific development, evaluation of bioavailability and efficacy in humans, and, finally, technical development and validation of the manufacturing process for regulatory approval. The technology is covered by an issued patent, currently owned by Chauvin Pharmaceuticals Ltd., of Groupe Chauvin, France [1].

The need for a drug delivery system that overcomes the major drawback in the use of eyedrops as simple aqueous solutions or suspensions, namely their very short residence time at the corneal surface, has been obvious for a long time. This led to the development of highly viscous formulations either as aqueous, polymer-based media or paraffinic ointments to increase the residence time, and hence the drug absorption.

II. OPHTHALMIC INSERTS

A logical extension of this idea was the introduction of solid inserts aimed at improved bioavailability and drug absorption, as well as avoiding antimicrobial preservatives and achieving accurate dosage. However, most of the earlier ocular solid inserts suffered from the twin disadvantages of complexity and difficulty

Copyright © 2003 Marcel Dekker, Inc.

of usage, particularly in self-administration and poor tolerability in the eye, mainly due to their rigidity and/or shape and size. Thus, they tended to fail to meet the most important criteria for effective ocular drug delivery systems.

In addition, some of these inserts were nonerodible, necessitating removal from the eye after the prescribed time span. Although there are advantages of predictable and controlled drug release rates and assurance of awareness by the patient of the insert in the eye throughout the time period, the "foreign body" sensation and the necessity for their removal at the end of the dosing period made nonerodible inserts particularly unattractive to patients.

In contrast, erodible (composed of either soluble or degradable matrices) ophthalmic inserts tend to have problems of inconsistency of drug release rates and bioavailability. However, they show much greater degrees of comfort and tolerability in the eye, compared to nonerodible inserts. Although attempts have been made to develop erodible inserts composed of water-soluble polymers such as hydroxypropylmethyl cellulose, none have achieved wide acceptance and popular usage. This has mainly been due to problems associated with sterile manufacture and presentation for handling and administration.

III. NODS

A. Concept and Design

The NODS was conceived with the aim of overcoming some of the problems associated with the earlier ocular insert systems, and to achieve greater ocular tolerability and ease of administration.

The scientific development of NODS encompassed two primary objectives, namely to present the system to the eye as a sterile, water-soluble, drug-loaded film and to serve as a unit-dose, preservative-free formulation for the delivery of a precise amount of the drug to the ocular surface. Any sustained drug release achieved as a result of the expected minimization of reflux tearing and drainage was considered to be an added benefit.

Thus, the basic design of NODS took the form of a three-component strip, consisting of a water-soluble, drug-loaded film attached, via a thin, water-soluble "membrane" film, to a thicker, water-soluble, "handle" film. All the above three films are made using the same grade of polyvinyl alcohol (PVA) in aqueous medium, but at three different concentrations. For ease and robustness in handling, the handle film is sandwiched between paper strips before the whole unit is sealed in a moisture-proof, paper/aluminum foil pouch. Typically, the drug-loaded film (also called "flag") is semicircular in shape (dimensions: 6 mm wide and 4 mm high) with a thickness of about 20 μm and a weight of about 500 μg. The thin membrane film is about 0.7 mm wide and 3–4 μm thick, while the handle

Copyright © 2003 Marcel Dekker, Inc.

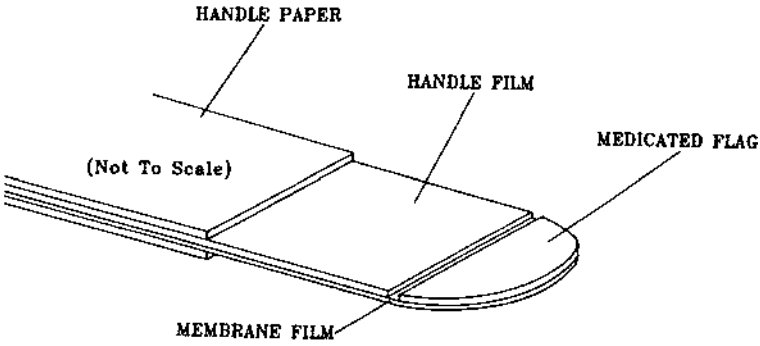


Figure 1 Diagrammatic representation of NODS technology.

film is about 30 μm in thickness. The shape and dimensions of the components of the device were optimized through evaluation by healthy human volunteers.

The choice of PVA as the material of construction of the NODS unit was made, after assessing a number of potential water-soluble polymers, based on its ability to form strong, but flexible, films without an added plasticizer, the capacity of its aqueous solutions to be heat-sterilized, and its widespread use and acceptance in ophthalmic formulations as a viscolyzer.

A representation of the NODS unit with its components is shown in Figure 1.

B. Application

In use, the NODS unit is removed from the pouch by holding the paper handle and is applied to the eye in such a manner that the drug film, membrane film, and a small portion of the handle film are placed in the lower conjunctival sac. On contact with the tear film, the membrane film dissolves rapidly (a few seconds) and the drug flag is detached from the rest of the device and released into the sac. The device, free of the drug film, can then be discarded. The drug film is hydrated by the tear film, allowing dispersion and dissolution, followed by drug diffusion and absorption.

C. Formulation and Manufacturing Process

As mentioned earlier, the three components of the NODS unit are made using the same grade of PVA, namely Gohsenol GH-17 with a mean molecular weight of 98,000 and about 88 mol% degree of hydrolysis. The PVA solutions of differ-

Copyright © 2003 Marcel Dekker, Inc.

ent strengths, including one for the "drug film" in which the drug is either dissolved or suspended as presterilized micronized powder, are prepared and sterilized in suitable pressure vessels. These are then coated onto a polyester film in the order in which they need to be in the NODS unit, dried and reeled up on a specially constructed coating machine.

Using a specially constructed cutting and packaging machine, the three-component film is attached to the top handle paper, delaminated from the supporting polyester film, attached to the bottom handle paper, cut into the NODS unit shapes, and packaged individually into the aluminum foil pouches.

The coating and cutting and packaging operations are carried out in a class 2 environment, using presterilized material and the sterile PVA solution, manufactured as described earlier.

Finally, the aluminum foil pouches, each containing an individual NODS unit, are terminally sterilized by gamma radiation. Thus, each NODS unit is able to be stored in a dry, sterile unit dose (preservative-free) format until opened for use.

IV. IN VIVO STUDIES

A. Gamma Scintigraphy in Human Volunteers

As mentioned earlier, the residence time at the ocular surface is a major determinant of the bioavailability, and hence the degree and extent of efficacy, of a topical dosage form. For this reason, studies were undertaken to establish the ocular surface residence characteristics of NODS "drug" film in human volunteers, by gamma scintigraphy using a gamma camera fitted with a pinhole collimator (to enable visualizing the surface of the eye). Two separate studies were undertaken:

1. in 10 human volunteers, using a PVA film incorporating technetium-99m (^{99m}Tc)-labeled sulfur colloid to reflect the residence time of the film itself and any insoluble drug contained in it [2], and
2. in 12 human volunteers, using a PVA film containing a ^{99m}Tc-labeled, water-soluble marker, namely diethylenetriaminepentaacetic acid (DTPA) to mimic the behavior of a soluble drug incorporated into the film [3].

In general, for these scintigraphic studies, three regions of interest (ROI), namely the cornea, inner canthus, and lacrimal duct, were delineated [3], as shown in Figure 2.

From the serial pictures taken through the gamma camera in the first study [2], it was observed that softening of the film and release of activity into the lower tear margin and the nasolacrimal sac occurred within the first 2 min, drainage

Copyright © 2003 Marcel Dekker, Inc.

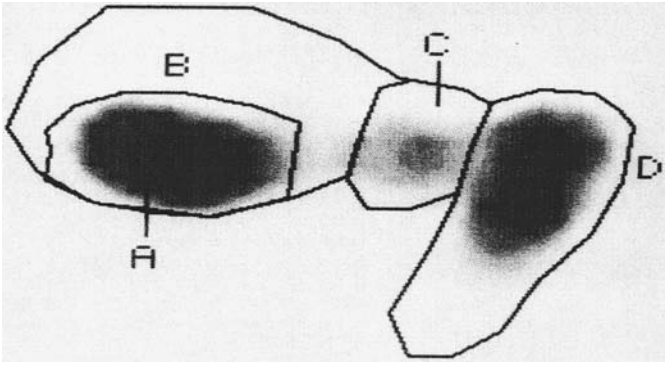


Figure 2 Regions of interest constructed on the summed gamma camera image: (A) NODS; (B) corneal surface; (C) inner canthus; (D) nasolacrimal duct.

and accumulation of the marker in the nasolacrimal duct following considerable dissolution of the film by about 7 min, and complete dissolution and appearance of the majority of the labeled marker in the nasolacrimal ROI by 13 min. The mean data from this study for the activity in the corneal ROI are shown in terms of percent remaining activity as a function of time in Figure 3. The mean half-time of clearance of the label from this ROI was calculated to be 9.2 ± 7.0 min, with obviously a large intersubject variation and range of 2–24 min.

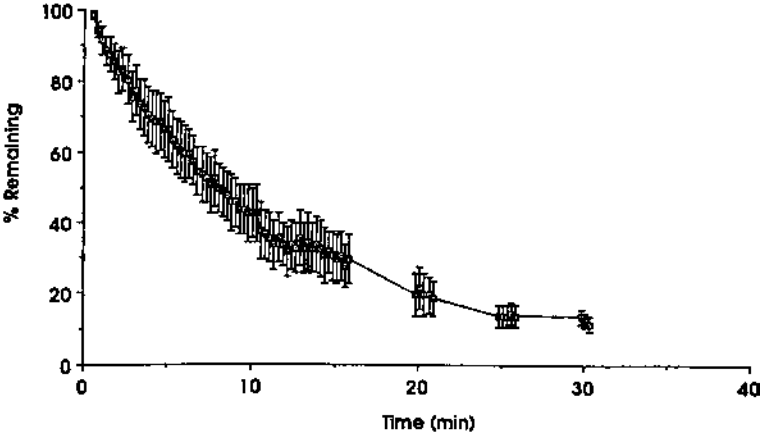


Figure 3 Clearance of ^{99m}Tc-labeled sulfur colloid from the corneal region of interest in humans (mean ± SE, $n = 10$).

Copyright © 2003 Marcel Dekker, Inc.

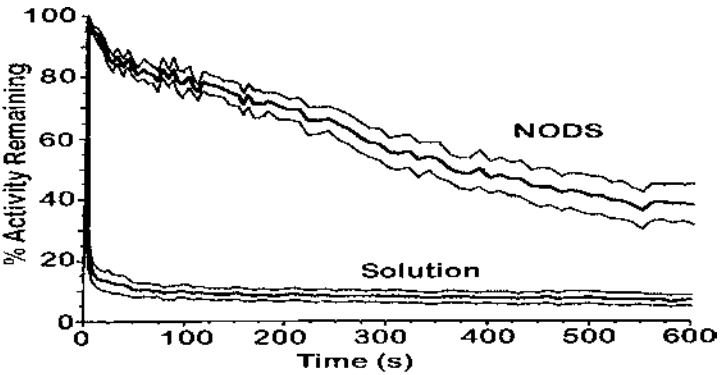


Figure 4 Precorneal residence of the radioactive marker after administration in a NODS unit or as a drop of a solution (mean ± SE, $n = 12$).

From the study with the soluble DTPA marker incorporated into either the PVA film or an aqueous solution medium [3], plots of mean clearance (± standard error of mean) are shown in Figure 4. The mean half-time of clearance of the label from the NODS and the corneal region together was found to be 406 ± 214 s, while that from the aqueous solution was 2.9 ± 1.5 s, this difference in clearance rates being significant at a level of $p < 0.001$.

B. Bioavailability and Efficacy in Human Subjects

1. Tropicamide

In a study in 12 human volunteers, one NODS unit, containing 125 μg of tropicamide or a drop of a 0.5% aqueous solution of tropicamide, was administered into one eye and a comparison was made of the degree of mydriasis, abolition of light reflex, and cycloplegia achieved [4].

For illustration, the results obtained for mydriasis are shown in Figure 5. NODS units showed a similar time for peak effect at 30–45 min, but a significantly longer duration of action at up to 7 h, compared to the aqueous solution. Similar results implying an enhanced bioavailability of the drug from NODS units were recorded for abolition of light reflex and cyclopegia.

2. Chloramphenicol

A study was reported of the time course of tear film concentrations in 12 human volunteers after administration of 125 μg of chloramphenicol as an eyedrop of 0.5% aqueous solution, as a 1% paraffinic ointment, or as a NODS film [5]. The

Copyright © 2003 Marcel Dekker, Inc.

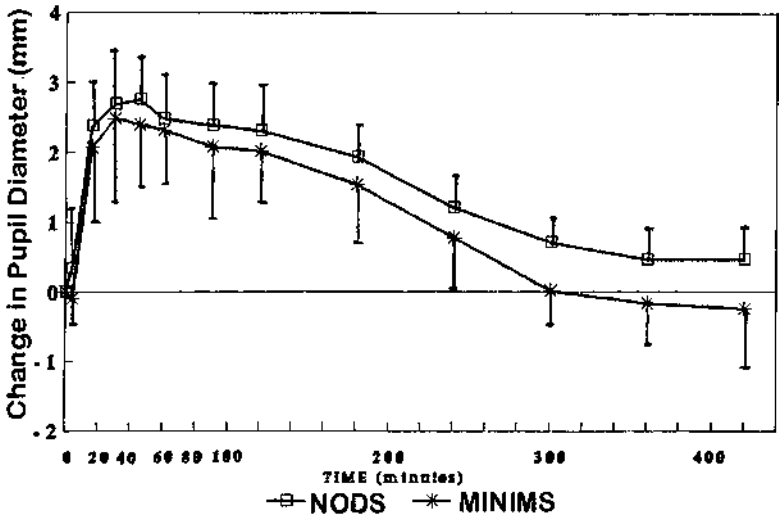


Figure 5 Mydriasis in human volunteers administered tropicamide either in NODS or as a solution. Change in pupil diameter (mean, $n = 12$).

results are shown in Table 1. From the results, the areas under the curve of the concentration of chloramphenicol in the tear film versus time were calculated and the relative bioavailabilities estimated as 6.5 for the ointment and 13.9 for the NODS film, relative to the eyedrop.

3. Pilocarpine

A study comparing the bioavailability of pilocarpine from NODS units with that from aqueous solution eyedrops in eight human volunteers has been reported [6]. NODS units containing 40 μg, 80 μg, or 170 μg and one drop of a 2% aqueous solution, corresponding to about 518 μg of pilocarpine nitrate, were administered, and the miotic and light reflex responses were recorded over 24 h. The mean miosis (pupillary constriction response) data for the eight volunteers are shown in Figure 6 as a function of time. The peak and area under the curve values for miosis and the percent light reflex inhibition values obtained for the eyedrop (518 μg of pilocarpine) were calculated to be equivalent to those for a NODS unit containing about 67 μg of pilocarpine, giving a relative bioavailability for NODS presentation of about 7.7. These data are shown in Table 2.

The above results were confirmed in the human volunteer study, mentioned earlier [3], wherein the pharmacological effects of a NODS film containing 63 μg of pilocarpine and a 25-μl drop of a 2% w/v solution of pilocarpine nitrate

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Mean Tear Film Concentrations of Chloramphenicol in Human Volunteers After Administration of 125 μg of Chloramphenicol as an Eyedrop of 0.5% Aqueous Solution, as a 1% Paraffinic Ointment, or as a NODS Film

Time after dosing (min)	Mean tear concentration of chloramphenicol (mg/L)		
	Eyedrop	Ointment	Film
2	689	414	1166
4	122	368	1000
8	42	505	1243
16	9	184	546
32	—	69	21
64	—	20	4

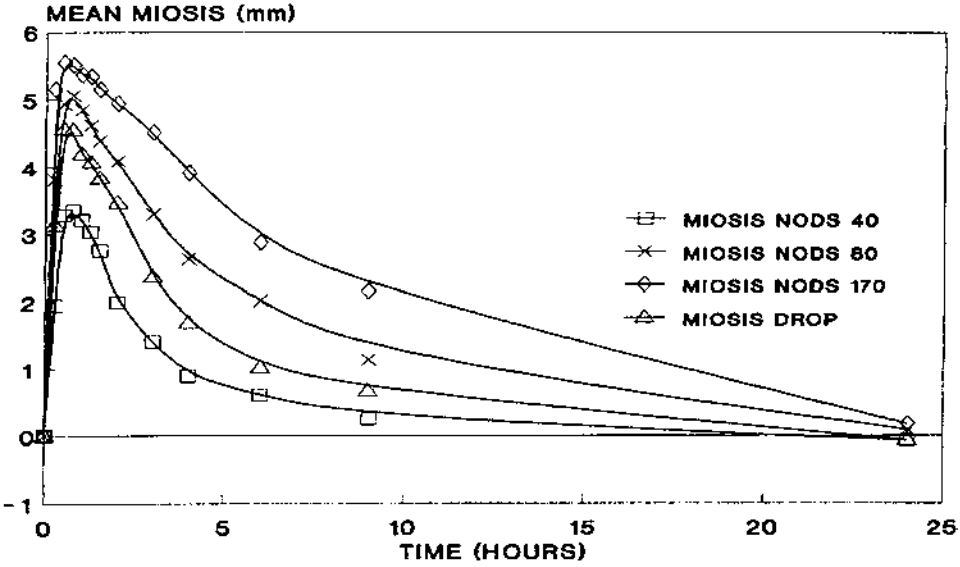


Figure 6 Mean pupillary constriction responses (miosis) to pilocarpine in human volunteers following application of NODS units containing 40, 80, or 170 μg or a drop of a 2% solution of pilocarpine ($n = 8$).

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Pilocarpine-Induced Peak Miosis, Total Response (area under the curve), and Light Reflex Inhibition Following Administration as NODS and Eyedrop Formulations[a]

	Peak miosis (mm)	AUC miosis (mm/h)	Light reflex inhibition (%)
NODS 40 μg	3.42 (0.58)	12.23 (2.78)	60.3 (8.8)
NODS 80 μg	5.07 (0.36)	33.78 (7.04)	88.2 (5.0)
NODS 170 μg	5.67 (0.38)	50.70 (7.34)	95.0 (1.7)
Eyedrop 2%	4.65 (0.47)	22.07 (4.78)	78.4 (4.1)
NODS equivalent of the eyedrop (μg)	67.1 (10.7)	65.6 (10.8)	68.5 (18.3)

[a] Values expressed as mean (±SEM).

(equivalent to 500 μg) were compared by monitoring changes in pupil diameter and intraocular pressure.

C. Ease of Administration

The following studies were undertaken to determine the acceptability of NODS to patients in self-administration and physicians in outpatient clinics [7]:

1. Self-administration by 201 healthy volunteers twice a day for 7 days and by 38 patients with primary open-angle glaucoma. In both cases, the majority preferred to use a mirror to aid in insertion and were successful after some experience. The NODS units were considered well tolerated, despite slight and brief foreign-body sensation.
2. A total of 174 patients received NODS tropicamide in both eyes, administered by 14 nurses and three ophthalmologists. The professionals found NODS units quick, easy, and acceptable in routine use, and the tolerability in patients was considered good, despite some initial discomfort on insertion.

V. REGULATORY ISSUES

Initially, marketing authorization applications were made in England for NODS tropicamide (125 μg) and NODS chloramphenicol (125 μg). The responses from the regulatory authorities indicated that additional information was required in terms of the following:

Copyright © 2003 Marcel Dekker, Inc.

1. Reproducibility of NODS units in batch manufacture with respect to dimensions, total weight, and drug content.
2. Since the drugs concerned were present as solid particles (added as micronized powder) in the PVA solutions used for coating as well as in the final NODS film, quantitative data on the particle size distribution, initially at manufacture and on storage testing.
3. Content uniformity for the drugs across individual units and subbatches, in addition to the average drug content of the units being within acceptable limits.
4. In general, validation of the whole process of manufacture and testing to demonstrate robustness of the procedures.

Some of the above considerations arose from the fact that NODS was a new drug delivery system with unique composition, manufacturing processes and, consequently, tests and methods.

It was possible to supply this information for NODS tropicamide after a considerable amount of further work at the pilot and manufacturing scale. This involved, among other actions, some modifications to the cutting and pouching machine to bring these processes under better control, and further testing for detailed and quantitative particle size distribution data on fresh and stored batches of NODS tropicamide. Eventually a license was granted and the product introduced into the market. This additional work helped in achieving better control over all the various stages of manufacture, and thus improved the level of quality assurance.

However, with chloramphenicol in NODS format, improved methods of chemical analysis showed a much higher level of degradation into both known and unknown products, mainly arising from the need to sterilize by gamma irradiation both the micronized drug powder and the final NODS units.

Further work has demonstrated that this problem of chemical decomposition through gamma irradiation is a major obstacle to the development of this system for many drugs in use.

VI. MARKETING

Although NODS tropicamide was introduced into the market at a price not significantly higher than that of the other unpreserved unit-dose eyedrop formulation, namely Minims tropicamide, it did not achieve the expected level of sales. This was partly because the product is only for diagnostic use, and many of the perceived benefits, such as absence of preservatives, improved bioavailability, and convenience of storage, were not sufficiently important in this context.

In addition, it was found that the transition from development phases to routine manufacture could not be achieved easily. The whole process turned out

Copyright © 2003 Marcel Dekker, Inc.

to be slow, intensive in the use of trained labor, and uneconomical in terms of productivity with the machines in use. As a result, the product was subsequently withdrawn from the market.

VII. FUTURE DEVELOPMENT

As mentioned earlier, the second product conceived in the NODS format, 125 μg of chloramphenicol, faced considerable difficulties in terms of chemical stability of the drug and had to be shelved. A similar situation with unacceptable levels of chemical degradation due to the need for sterilization of the drug compound and finished NODS units by gamma irradiation was faced with other potential drugs. The whole project had to be suspended for this reason.

Despite the above setbacks, the basic concept and design of the dosage form have many attractive attributes. If new technologies and processes can be devised to overcome the problems of chemical stability and to improve the speed, accuracy, and robustness of the processes of manufacture, the NODS technology can be converted into an effective drug delivery system for both instant and sustained drug delivery to the eye.

REFERENCES

1. R Lloyd. Applicators for pharmacologically active agents, their preparation and use. UK patent 2,097,680, 1985.
2. P Fitzgerald, CG Wilson, JL Greaves, M Frier, D Hollingsbee, D Gilbert, M Richardson. Scintigraphic assessment of the precorneal residence of new ophthalmic delivery system (NODS) in man. Int J Pharm 83:177–185, 1992.
3. JL Greaves, CG Wilson, AT Birmingham, PH Bentley, M Richardson. Scintigraphic studies on the corneal residence of a new ophthalmic delivery system (NODS): rate of clearance of a soluble marker in relation to duration of pharmacological action of pilocarpine. Br J Clin Pharmacol 33:603–609, 1992.
4. MC Richardson. An investigation of tropicamide NODS compared with tropicamide solution in human volunteers. Poster at the 9th Pharmaceutical Technology Conference, Veldhoven, The Netherlands, 1990.
5. DA Hollingsbee, K Hughes, D Gilbert. A comparison of the human ocular bioavailability of chloramphenicol administered as a solution, an ointment and a water soluble polymeric film insert. Poster at the International Symposium on Ophthalmic Drug Delivery, Pisa, Italy, 1986.
6. JA Kelly, PD Molyneux, SA Smith, SE Smith. Relative bioavailability of pilocarpine from a novel ophthalmic delivery system and conventional eye drop formulations. Br J Ophthalmol 73:360–362, 1989.
7. MC Richardson, PH Bentley. A new ophthalmic delivery system. In: AK Mitra, ed. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993, pp. 355–367.

Copyright © 2003 Marcel Dekker, Inc.

28

Bioadhesive Ophthalmic Drug Inserts (BODI)

Olivia Felt-Baeyens and R. Gurny
University of Geneva, Geneva, Switzerland

I. INTRODUCTION

Based on their characteristics of solubility, bioadhesive ophthalmic drug inserts (BODI), patented by Gurtler and Gurny [1] in 1993, belong to the group of soluble inserts made of synthetic and semisynthetic polymers.

The major composition of BODI inserts consists of a ternary mixture of hydroxypropylcellulose (HPC), ethylcellulose (EC), and carbomer (Carbopol® 934P) (CP) (Table 1). The replacement of natural polymers such as collagen by synthetic polymers is undoubtedly advantageous regarding their safety of use. Indeed, natural biopolymers may be associated with inflammatory response in the ocular tissues due to the presence of residual proteins. In addition, at present, devices based on collagen may encounter difficulties in being accepted by regulatory authorities, because of possible prion infection.

The rationale for developing inserts endowed with bioadhesive properties using Carbopol was based on the observation that available ocular inserts did not always allow prolonged release of the incorporated drugs and may be displaced or sometimes expelled by eyeball movements. Despite the fact that the use of nonneutralized CP is controversial due to its acidic nature possibly inducing eye irritation, Gurtler et al. [2] have demonstrated that it does not cause any damage to the ocular surface at concentrations up to 3%.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Polymeric Composition of BODI

Polymer	HPC	EC	CP
Characteristic	Hydrophilic	Hydrophobic	Bioadhesive
Type	Klucel® HXF NF	Ethocel® N50 NF	Carbopol® 934P
Role	Main vehicle ensuring aqueous solubility	Reduce insert deformation	Reduce risk of expulsion
Concentration (% w/w)	67.0	30.0	3.0

II. DESCRIPTION OF BODI TECHNOLOGY

A. Size and Shape

BODIs are rod-shaped inserts obtained by the extrusion of a dried homogeneous powder mixture composed of the polymeric vehicle and the active compound using a specially designed ram extruder. Their final optimal dimensions, adapted for placement into the inferior lateral conjunctival cul-de-sac of animals like rabbits or dogs, are 5.0 mm in length, 2.0 mm in diameter, and 20.5 mg in weight. It should be noted that these parameters are of primary importance since Baeyens et al. (unpublished data) found that a slight increase in one of these parameters resulted in an increase in rate of expulsion.

B. Manufacture

To ensure a homogeneous distribution of the drug in the matrix, a double extrusion process has been demonstrated to be necessary [2]. Briefly, the following manufacturing conditions were applied: an extrusion temperature of 140–160°C, a warming-up time of 2 min, and an extrusion pressure of 200–300 kPa. The technique of extrusion offers some advantages such as cost-effectiveness, rapid development, and good reproducibility.

III. RESEARCH AND DEVELOPMENT STUDIES

A. Initial Development Results

The first developed BODIs contained gentamicin sulfate, an aminosidic antibiotic, as a model drug [3,4]. However, despite good pharmacokinetic performance when compared with conventional formulations such as eyedrops, it was demonstrated by Baeyens et al. [5] that due to its high hydrophilicity, gentamicin was

Copyright © 2003 Marcel Dekker, Inc.

almost immediately released from BODI. This led to a period of efficacy often less than 12 h, similar to ocular inserts based on gelatin [6] or collagen [7–9]. Therefore, Baeyens et al. [5] studied different approaches to reduce the solubility of gentamicin using cellulose acetate phthalate (CAP) to obtain either a solid dispersion or a coprecipitate (Fig. 1).

Results showed that CAP was a good release moderator since the time of efficacy was significantly increased after gentamicin pretreatment (Table 2). However, it can also be seen from the results in Table 2 that BODI 3 was less effective than BODI 2 in prolonging gentamicin release. On the basis of a modified Draize test, the authors correlated this difference with the poor tolerance (Fig. 2) following the deposition of BODI 3 in the inferior cul-de-sac of rabbits, probably owing to the presence of surfactants in Aquateric®, which are well known for their irritating potential.

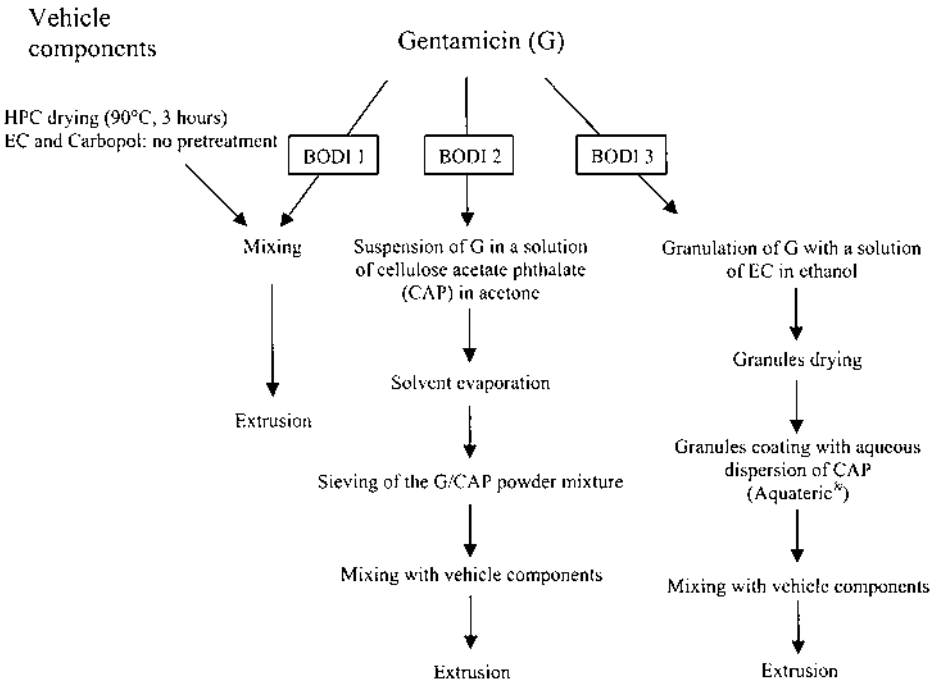


Figure 1 Schematic representation of the fabrication processes of BODIs containing unmodified (BODI 1) or modified gentamicin by the solid dispersion technique (BODI 2) or by the coprecipitate technique (BODI 3).

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Half-Life Time of Elimination ($t_{1/2}$) and Time of Efficacy (t_{eff}) of Gentamicin After Deposition of Insert (BODI 1, 2, or 3) in Rabbit Eye

Insert	Gentamicin state	$t_{1/2}$ (hr)	t_{eff} (hr)
BODI 1	Unmodified	5.11	11.9 ± 0.1
BODI 2	Solid dispersion	21.92	43.8 ± 6.0
BODI 3	Coprecipitate	12.29	23.3 ± 0.3

Source: Adapted from [5].

B. Further Developmental Studies

From a therapeutic viewpoint, BODIs further evolved in 1998 by coformulation of a second active compound, namely dexamethasone phosphate with gentamicin [10,11]. The rationale behind coformulating a corticosteroid with an antibacterial agent into a single ophthalmic drug delivery system was based upon the recommendation that, in the case of external infections such as keratitis or conjunctivitis, coadministration of a steroid limits the structural damage related to the inflammatory response [12].

The main goals of this approach were (a) to avoid the need for separate administration of dexamethasone and (b) to limit the side effects associated with

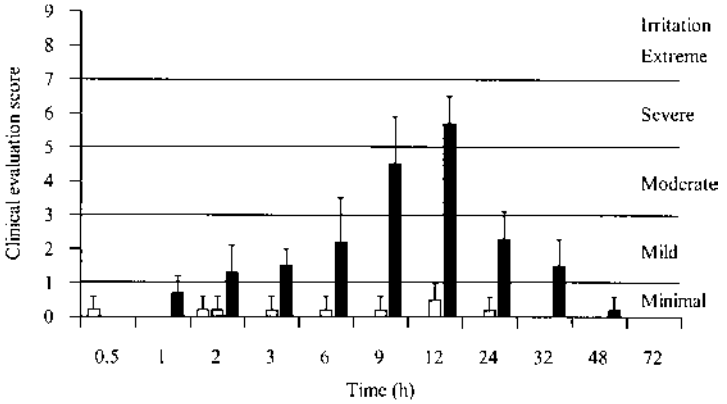


Figure 2 Comparative clinical evaluation of irritation scores after deposition of inserts containing (□) gentamicin without pretreatment (BODI 1), (⊡) solid dispersion of gentamicin with CAP (BODI 2), and (■) coprecipitate of gentamicin with CAP (BODI 3). (Adapted from [5].)

Copyright © 2003 Marcel Dekker, Inc.

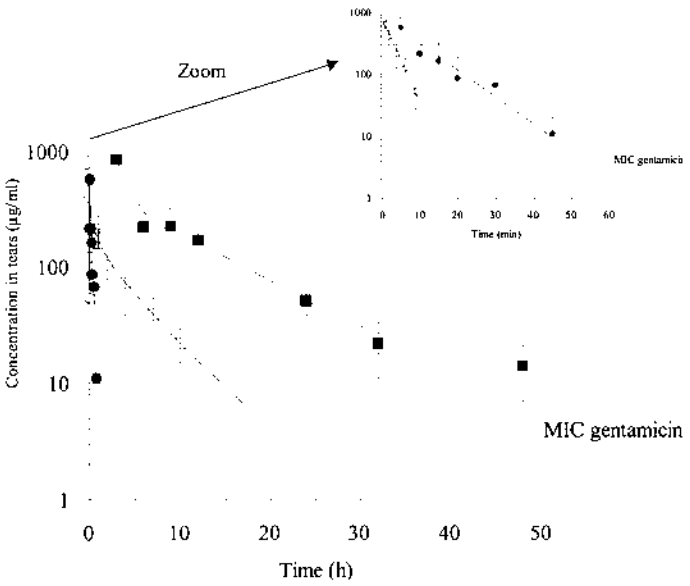


Figure 3 Gentamicin sulfate (■,●) and dexamethasone phosphate (□,○) profiles in tear fluid after deposition of one insert (squares) or after administration of 50 µL of a collyrium (circles) containing an association of both active ingredients (tested in rabbit, mean ± SEM, $n = 6$). (Adapted from [10,11]).

repeated installations of dexamethasone, particularly the risk of increased intraocular pressure leading to glaucoma.

These inserts successfully provided a prolonged release of gentamicin above its MIC value for nearly 50 h, while a suitable immediate release of dexamethasone in tears for about 12 h was simultaneously achieved (Fig. 3).

C. Mechanism of Drug Release

Both gentamicin and dexamethasone show a biphasic release profile from a BODI matrix when inserted into the eye. Indeed, the release of drugs from the BODI systems is characterized by two phases [13]: the first one corresponds to the penetration of tear fluid into the insert inducing a high release rate of drug by diffusion and forming a gel layer around the core of the insert. This external gelification then induces the second period, which corresponds to a slower release rate, but which is still controlled by a diffusion mechanism. This drug release mechanism from BODI still remains hypothetical since no in vitro tests have been conducted to confirm the mechanism.

Copyright © 2003 Marcel Dekker, Inc.

D. Current Developmental Studies

Because previous investigations on BODI successfully demonstrated that it was very well tolerated and provided good pharmacokinetic results, the technology is currently being studied in clinical trials on beagle dogs for the treatment of conjunctivitis, keratoconjunctivitis, or superficial corneal ulcers (unpublished data). Initial results are encouraging, with the placement of a single BODI achieving a similar clinical effect as a therapeutic regimen based on the instillation of 1 drop of a commercial collyrium 3 times per day over 7 days of treatment.

E. Future Developmental Studies

Future studies using the BODI technology may be directed toward the evaluation of other active compounds for ocular therapy. However, it must be noted that the fabrication process limits the choice of therapeutic agents to those that are not heat sensitive.

Another future development of the BODI technology may be to extend its use from its original veterinary applications to human applications. This would involve some design modifications, especially regarding the size and shape of the inserts.

To acquire data that are more comprehensive on this promising technology, complementary studies may be considered such as: (a) evaluation of the effect of the extrusion technique on the stability of the various components of BODI (mainly molecular weight of the polymers), and (b) the effect of a sterilization process on the stability of the formulation components. In the case of the latter, since BODI contains an antibacterial agent and is fabricated at high temperature, it has previously been concluded that inserts were pathogen free. However, it has not been demonstrated using official tests, such as those described in the European Pharmacopoeia, that these two parameters ensure a comparable level of sterility compared to an actual sterilization process such as gamma-sterilization.

IV. CONCLUSION

BODI are rod-shaped soluble inserts made of synthetic and semisynthetic polymers. The use of synthetic polymers offers advantages with regard to safety. Inclusion of the bioadhesive excipient Carbopol allows for prolonged release of incorporated drugs and increases residence time of the delivery system in the eye.

BODI inserts are obtained by an extrusion process that offers some manufacturing advantages, but the high extrusion temperatures limit drug candidates to those that are heat stable.

Several drugs have been incorporated into BODI inserts resulting in release profiles measured in hours to days.

Copyright © 2003 Marcel Dekker, Inc.

Further studies are currently being performed on this promising ophthalmic technology and future studies may see it extended to human applications.

REFERENCES

1. F Gurtler, R Gurny. Insert ophtalmique bioadhésif. European patent 934 00677–61, 1993.
2. F Gurtler, V Kaltsatos, B Boisramé, R Gurny. Development of a novel soluble ophthalmic insert: evaluation of ocular tolerance in rabbits. Eur J Pharm Biopharm 42: 393–398, 1996.
3. F Gurtler, V Kaltsatos, B Boisramé, R Gurny. Long-acting soluble bioadhesive ophthalmic drug insert (BODI) containing gentamicin for veterinary use: optimization and clinical investigation. J Control Rel 33:231–236, 1995.
4. F Gurtler, V Kaltsatos, B Boisramé, J Deleforge, M Gex-Fabry, LP Balant, R Gurny. Ocular availability of gentamicin in small animals after topical administration of a conventional eye drop solution and a novel long acting bioadhesive ophthalmic drug insert. Pharm Res 12:1791–1795, 1995.
5. V Baeyens, V Kaltsatos, B Boisramé, M Fathi, R Gurny. Evaluation of soluble bioadhesive ophthalmic drug inserts (BODI) for prolonged release of gentamicin: lacrymal pharmacokinetics and ocular tolerance. J Ocul Pharmacol Ther 14:263–272, 1998.
6. PI Punch, DH Slatter, ND Costa, ME Edwards. Investigation of gelatin as a possible biodegradable matrix for sustained delivery of gentamicin to the bovine eye. J Vet Pharmacol Ther 8:335–338, 1985.
7. FQ Liang, RS Viola, M DelCerro, JV Aquavella. Non cross-linked collagen discs and cross-linked collagen shields in the delivery of gentamicin to rabbit eyes. Invest Ophthalmol Vis Sci 33:2194–2198, 1992.
8. RB Phinney, D Schwartz, DA Lee, BJ Mondino. Collagen-shield delivery of gentamicin and vancomycin. Arch Ophthalmol 106:1599–1604, 1988.
9. SE Bloomfield, T Miyata, MW Dunn, N Bueser, KH Stenzel, AL Rubin. Soluble gentamycin ophthalmic inserts as a drug delivery system. Arch Ophthalmol 96:885–887, 1978.
10. V Baeyens, V Kaltsatos, B Boisramé, E Varesio, J-L Veuthey, M Fathi, LP Balant, M Gex-Fabry, R Gurny. Optimized release of dexamethasone and gentamicin from a soluble ocular insert for the treatment of external ophthalmic infections. J Control Rel 52:215–220, 1998.
11. R Gurny, V Kaltsatos, V Baeyens, B Boisramé. Therapeutic or hygienic compositions with controlled and prolonged release of the active principles, in particular for ophthalmic use. WO 98/56346, 1998.
12. GA Stern, M Buttross. Use of corticosteroids in combination with antimicrobial drugs in the treatment of infectious corneal disease. Ophthalmology 98:847–853, 1991.
13. F Gurtler, R Gurny. Patent literature review of ophthalmic inserts. Drug Dev Ind Pharm 21:1–18, 1995.

Copyright © 2003 Marcel Dekker, Inc.

29
Oral Mucosal Drug Delivery

Ian W. Kellaway
School of Pharmacy, University of London, London, England

Gilles Ponchel and D. Duchêne
UMR CNRS 8612 and University of Paris XI, Châtenay-Malabry Cedex, France

I. INTRODUCTION

This chapter considers both local and systemic delivery of drugs and discusses drug delivery systems that are applied to a variety of sites of the oral cavity including the gingiva, buccal, sublingual, and periodontal pocket.

The mucosa of the mouth is very different from the rest of the gastrointestinal tract and morphologically is more similar to skin. Although the permeability of skin is widely regarded as poor, it is not generally appreciated that the oral mucosa lacks the good permeability demonstrated by the intestine. These differences within the gastrointestinal tract can largely be attributed to the organization of the epithelia, which serve very different functions. A simple, single-layered epithelium lines the stomach, small intestine, and colon, which provides for a minimal transport distance for absorbents. In contrast, a stratified or multilayered epithelium covers the oral cavity and esophagus and, in common with skin, is composed of layers with varying states of differentiation or maturation evident on progression from the basal cell layer to the surface.

Drugs have been applied to the oral mucosa for topical applications for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. Notwithstanding the relatively poor permeability characteristics of the epithelium, a number of advantages are offered by this route of administration. Foremost among these are the avoidance of first-pass metabolism, ease of access to the delivery site, and the

Copyright © 2003 Marcel Dekker, Inc.

opportunity of sustained drug delivery predominantly via the buccal tissues. Delivery can also be terminated relatively easily if required. The robustness of the epithelium necessary to withstand mastication also serves the drug delivery process well as fast cellular recovery follows local stress and damage.

Indeed the two most challenging issues to be addressed in the oral mucosal delivery of drugs are undoubtedly permeability enhancement and dosage form retention at the site of application. The continuous secretion of saliva and its subsequent swallowing can lead to substantial drug depletion from the dosage form and hence low bioavailability.

Before considering some of the more recent approaches to the design of dosage forms and devices for oral mucosal drug delivery that appear in the chapters in this part of the book, it is pertinent to consider the nature of the barrier afforded to this route of delivery and some of the historical approaches taken to develop drug delivery systems for use in the oral cavity.

II. STRUCTURE AND FUNCTION OF ORAL MUCOSA

A stratified, squamous epithelium lines the oral cavity. Three different types of oral mucosa can be identified, i.e., masticatory, lining, and specialized mucosa (Fig. 1). The masticatory mucosa covers the gingiva and hard palate. It comprises a keratinized epithelium strongly attached to underlying tissues by a collagenous connective tissue and as such is able to withstand the abrasion and shearing forces of the masticatory process. The lining mucosa covers all other areas except the dorsal surface of the tongue and is covered by a nonkeratinized and hence more permeable epithelium [1]. This mucosa is capable of elastic deformation and hence stretches to accommodate speech and mastication requirements. The epithelium in humans varies in thickness according to the region, e.g., floor of the mouth, 190 μm; hard palate, 310 μm; buccal, 580 μm [2]. A loose, elastic connective tissue attaches the lining mucosa to underlying structures. The specialized mucosa of the dorsum of the tongue is characteristic of both the masticatory and lining mucosa in that it consists of epithelium partly keratinized and partly nonkeratinized. This epithelium is bound to the muscle of the tongue.

The regional differences in morphology result in different permeability characteristics that have considerable influence on the design and siting of drug delivery systems. The differentiation process that gives rise to the regional differences occurs as the keratinocytes migrate from the buccal layers to the epithelial surface. Within the basal layer the keratinocytes are cuboidal or columnar with a surrounding plasma membrane and containing the usual intracellular organelles. A constant population of epithelial cells is maintained by the division of the basal keratinocytes at a rate equating to the desquamation of surface cells. Aging and disease can result in a loss of this balance, which can lead to a thickening (hyper-

Copyright © 2003 Marcel Dekker, Inc.

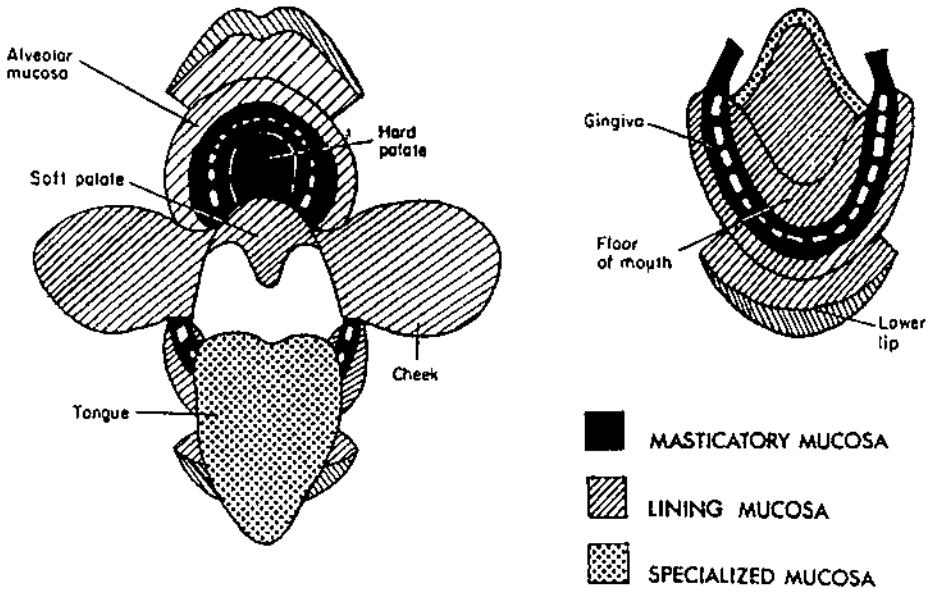


Figure 1 The distribution of masticatory, lining, and specialized mucosae within the oral cavity.

trophia) or thinning (atrophia) of the epithelium. The media turnover time is slower for keratinized tissue, e.g., hard palate 24 days, than nonkeratinized, e.g., buccal mucosa 13 days [3]. Also relevant to the development of drug delivery systems are the surface areas of the human mouth occupied by keratinized (50%) and nonkeratinized (30%) tissues. Percentages are expressed with reference to the total surface area of the mouth [4].

In nonkeratinized epithelium, the morphological changes upon differentiation are less than for keratinized tissue. Also there is less accumulation of lipids and cytokeratins in the keratinocytes. Mature cells become larger and flatter exhibiting a protein envelope, nuclei, and other organelles. There is no tendency for aggregation of the cytokeratins as is evident in keratinized tissue and the glycogen content increases.

Desmosomes are still present between cells in the surface cell layer where intercellular spaces are both wide and irregular. Membrane-coating granules appear as approximately 200-nm spheres in the prickle cell layers [5,6], which subsequently fuse with cell membranes to discharge their contents in the superficial cell layer.

Copyright © 2003 Marcel Dekker, Inc.

Some of the membrane-coating granules contain lamellae, which upon discharge may give rise to short stacks of lamellar lipid observed in the intercellular spaces in the outer layers of the epithelium [7]. The majority, however, are amorphous. Also present in the granules are hydrolytic enzymes [8,9] and glycoconjugates, probably glycoproteins and glycolipids [7,10]. Evidence suggests that the intercellular permeability barrier arises from the discharged contents of the membrane-coating granules.

III. NATURE OF THE LIPID BARRIERS

Phospholipids, cholesterol, and glycosyl ceramides predominate [11] with the phospholipid fraction composed of sphingomyelin and phosphatidyl-choline, -ethanolamine, -serine, and -inositol. Triglycerides and cholesterol esters are also present with traces of fatty acids and ceramide. This lipid cocktail may well give rise to fluid lamellae.

IV. BLOOD FLOW

The blood flow through a tissue is important for achieving good drug absorption. The external carotid artery is the main source of blood supply to the oral tissues. It branches into the maxillary, supplying the hard palate and cheeks, the lingual, supplying the tongue, sublingual, and gingival areas, and the facial artery, supplying blood to the soft palate and lips. Blood from the capillary beds is collected by three principal veins that flow into the internal jugular vein. Even during disease, blood flow through human oral mucosa is believed to be sufficiently fast as not to be rate-limiting in drug absorption.

V. SALIVA AND MUCUS

Saliva is essentially a protective fluid for the tissues of the oral cavity. The major component of the mucous secretions are the soluble mucins that can associate to form oligomeric mucins. These structures provide both viscoelastic and lubricating properties. Salivary mucins have a number of host-defense functions including the establishment of a permeability barrier overlying the epithelia, lubrication of surface tissues, and modulation of the colonization of oral microorganisms.

Approximately 750 mL of saliva is produced daily in an adult [12,13] with 60% from the submandibular glands, 30% from the parotids, $<5\%$ from the sublingual glands, and around 6% from the minor salivary glands found beneath the

Copyright © 2003 Marcel Dekker, Inc.

epithelium in most regions of the oral mucosa. Saliva is a mixture of serous secretions, which are high in glycosylated protein of low viscosity, and mucus secretions, which have a higher carbohydrate-to-protein ratio and little to no enzymatic activity. The parotids produce almost entirely serous secretions, the submandibular largely mucous secretions, while the sublingual glands produce a mixed serous/mucous secretion. Up to 70% of the total saliva mucin content arises from the minor salivary glands [14].

Saliva contains a variety of esterases (mainly carboxylesterases) (e.g., [15]) that may hydrolyze susceptible drug ester groups. The mode of administration of tablets for the oral transmucosal delivery of drugs and their disintegration rate were shown to influence saliva secretion and, because of the link between esterase activity and saliva flow rate [16], saliva esterase activity [17].

The pH of saliva has been reported to vary between 6.5 and 7.5 [12,13] with the principal buffering function ascribed to the bicarbonate system and to a lesser extent phosphate and protein buffers. Control of saliva pH in localized areas may be considered to optimize the transcellular absorption of ionizable drugs, i.e., by promoting the presence of the un-ionized species. Salivary film thickness has been estimated to be between 0.07 and 0.10 mm [4] and the mucins within this film may permit the attachment of delivery systems such as patches by the employment of mucoadhesive polymers. Interfacial mixing of the polymer with the mucin allows the establishment of secondary bonds and hence retention of the dosage form at the delivery site. The extent to which such adhesion stimulates further flow of mucus from the occluded minor salivary glands is unclear. The mucus film may act as a further barrier to the absorption of drugs.

VI. THE ABSORPTION BARRIER

For some drugs a considerable barrier contribution arises as a result of presystemic metabolism. For drugs not subject to such metabolism, the principal barrier is provided by the oral mucosa. The mucus film may act as a barrier, although unless the drugs bind specifically with the mucins or are large molecules ($>$ 1 kDa), the diffusion through the mucus is not a rate-determining step.

For keratinized epithelium, the major diffusional barrier is encountered in the upper keratinized layer, which results in lower permeability coefficients compared with nonkeratinized tissue. However, for large hydrophilic species such as horseradish peroxidase [18] or lanthanum [19], only minor differences have been reported for permeability coefficients between keratinized and nonkeratinized tissues.

Permeability rates of solutes will depend on their molecular characteristics, e.g., size, lipophilicity, and extent of ionization. There are two principal routes of penetration: transcellular and paracellular (intercellular). A compound may

Copyright © 2003 Marcel Dekker, Inc.

access both these routes, although one is generally preferred according to the physicochemical properties of the compound. The paracellular route is the principal route for hydrophilic compounds whereas for lipophilic molecules the transcellular route predominates.

VII. ORAL MUCOSAL DOSAGE FORMS

The design of efficient delivery systems intended for the systemic delivery of drugs through the oral mucosa or for local delivery results from a compromise between the need for an important absorptive surface and the necessity to maintain a high drug concentration at this site. Owing to the specific physiological features of the oral cavity, these delivery systems can be designed for developing a contact area with either the largest mucosal surface or a restricted portion of the mucosa.

In this respect, and depending on their design, solid dosage forms offer versatile possibilities for modulating drug delivery. On the one hand, a large mucosal contact area favors drug absorption. This can be obtained through the use of conventional tablets or fast-dissolving tablets that produce rapidly concentrated saliva drug solutions, able to coat the oral mucosa easily. However, such systems are likely to be accidentally expulsed or progressively swallowed and this phenomenon is likely to counterbalance the gain in drug absorption due to the high contact area. On the other hand, a restricted contact area allows for not only the localization of the drug delivery system at an optimal site for drug absorption, but also the design of controlled-delivery systems. Obviously, mucoadhesive tablets or mucoadhesive patches can achieve this goal and restrain uncontrolled leakage of the drug in the lumen of the oral cavity and subsequent elimination.

A. Design of Solid Oral Dosage Forms According to Their Mobility in the Oral Cavity

Solid oral dosage forms can be classified according to their mobility in the oral cavity [20]. Typically, two types of systems can be described: (a) nonattached or mobile solid oral dosage forms that would be physically maintained within the oral cavity in contact with the mucosal surface by a conscious effort of the patient, and (b) attached or immobilized drug delivery systems that can be retained on the mucosal surface by the adhesive properties of the system itself. Conventional tablets and fast-dissolving tablets belong to the first category. Following their administration, such formulations must be kept in contact with the mucosal area by a conscious effort of the patient because such formulations are mobile. Therefore, several factors are expected to decrease their effectiveness:

Copyright © 2003 Marcel Dekker, Inc.

(a) the residence time of such formulations is generally very short because of their removal from the oral cavity following swallowing, (b) high inter- and intra-individual variability in bioavailability can be expected with these formulations due to modification of delivery rates by physiological factors, e.g., tongue and cheek movements or variable salivary secretion, and (c) released drug is not protected from the potentially degrading environment of the oral cavity. However, despite these limitations, these delivery systems have been shown to be clinically efficient for the administration of drugs that are easily absorbed through the mucosa and/or are not degraded in the oral cavity.

The second category deals with attached or immobilized drug delivery systems that can be retained on the mucosal surface for a prolonged period of time by the adhesive properties of the system itself. Such systems offer advantages over nonattached systems. These include: (a) the immobilization allows an intimate contact to be developed between the dosage form and the mucosa; (b) a high drug concentration can be maintained at the absorptive surface for a prolonged period of time; (c) the dosage form can be immobilized specifically at any part of the oral mucosa: buccal, labial, sublingual, or gingival mucosa; and (d) the system itself can protect the drug from environmental degradation.

As early as 1847, Sobrero reported that nitroglycerine was absorbed from the oral cavity from solutions [21]. Since that time, various drug delivery systems belonging to these two categories have been proposed for clinical applications. Table 1 gives an overview of some commercially available solid dosage forms. Most of them are fast-releasing dosage forms including fast-dissolving tablets and lyophilized systems (e.g., Expidet®, Lyocs®). However, controlled-release

Table 1 Some Commercially Available Solid Dosage Forms for the Systemic Delivery of Various Drugs by the Oral Mucosal Route

Drug	Proprietary name/manufacturer	Dosage form
Nitroglycerin	Nitrostat®, Parke Davis Susadrin®, Forest	Tablet
Isorbide dinitrate	Risordan®, Rhône-Poulenc Rorer	Bioadhesive tablet
Erythrithyle trinitrate	Cardiwell®, Wellcome	Tablet
Nifedipine	Adalat®, Bayer	Tablet
Buprenorphine	Temgesic®, Reckitt & Colman	Tablet
Apomorphine, HCl	Apomorphine®, Chabre	Tablet
Prochlorperazine	Buccastem®, Reckitt & Colman	Bioadhesive tablet
Phloroglucinol	Spasfon-Lyoc®, Lafon	Lyocs
Oxazepam	Seresta Expidet®, Wyeth	Lyophilized tablet
Lorazepam	Temesta Expidet®, Wyeth	Lyophilized tablet
Methyltestosterone	Metandren®, Ciba-Geigy	Tablet

Copyright © 2003 Marcel Dekker, Inc.

systems are progressively being clinically experimented and launched on the market, including bioadhesive tablets and patches. Their advantages and limitations will be discussed further.

B. Conventional Tablets

Traditionally, systemic administration by the oral route was restricted to a very limited series of drugs, such as glyceryl trinitrate and some steroids. Consequently, solid dosage forms suited for oral delivery were derived from those used for the oral route and more or less adapted to some of the specific features of the oral cavity. Conventional tablets have been used since the end of the nineteenth century. They are rather unsophisticated dosage forms for delivery to the oral cavity. However, they are easy to manufacture and can be produced by standard manufacturing techniques. However, as discussed above, several factors tend to decrease their performance. Those factors make conventional tablets unsatisfactory for systemic delivery via the oral mucosa of many drugs.

Conventional tablets or molded tablets have been mostly proposed for administration via the sublingual route. For example, fentanyl has been incorporated in such a system and has been shown to produce reliable sedation and anxiolysis when administered prior to a surgical operation in children [22]. The rate of disintegration of such tablets must be carefully considered. For example, in the case of nitroglycerine, in vivo availability from fast-disintegrating tablets composed of soluble excipients (lactose, mannitol, sucrose) were shown to be strongly dependent upon disintegration rates [23,24].

C. Accelerated-Release Solid Oral Mucosal Dosage Forms

When drug permeability is high, and if fast absorption is required, it has been proposed that it can be advantageous to very rapidly create in the buccal cavity a highly concentrated drug solution that gains contact with a large mucosal surface. In accord with this concept, specialized solid oral mucosal dosage forms have been designed such as fast-dissolving tablets and lyophilized tablets.

Fast-dissolving molded tablets have been developed consisting of drug and polyethyleneglycol blends with a melting point around body temperature. Such delivery systems have been investigated for the delivery of nitroglycerin [23,24] and progesterone [25].

As an alternative to this approach, dosage forms prepared by freeze-drying viscous solutions of different sugars have been proposed and marketed under the trade name Lyocs (Table 1).

More recently, a freeze-dried mixture of oxazepam and lorazepam, fast-dissolving excipients, and a radiotracer (micronized radiolabelled ion exchange resin) (Expidet) has been investigated. Wilson et al. [26] measured the clearance,

Copyright © 2003 Marcel Dekker, Inc.

residence time, and distribution pattern of this dosage form in humans by using gamma-scintigraphy following its application at the surface of the tongue. The formulation was observed to completely dissolve within 15 s. They reported that the clearance of 50% of the formulation from the oral cavity was, respectively, 190 s and 50 s depending upon the amount of ion exchange resin incorporated into the dosage form (2.5 mg and 10 mg, respectively). The extent of absorption of oxazepam and lorazepam from the oral cavity was estimated by measuring the amount remaining in the mouth by performing buccal washings. At each of the time points investigated (30, 60, 90, and 120 s), about 90% of drug was recovered, suggesting that negligible absorption of the drug took place during the time that the formulation was in contact with the tongue. Therefore, such a system may prove useful only if the drug is rapidly absorbed. The results suggest that for such oral mucosal drug delivery systems it is necessary to carefully balance the rate of drug delivery with the rate of drug absorption.

D. Controlled-Release Solid Oral Dosage Forms

The two last decades have been marked with a renewal of interest in the delivery of drugs to the oral cavity, which cannot be adequately delivered by more conventional routes. For many drugs, including some biologically active peptides, the oral mucosal route has been regarded as an alternative to unsatisfactory oral or parenteral administration. Considerable attempts have been made to develop efficient dosage forms able to improve patient compliance, to improve drug bioavailability, to control drug delivery and appearance in the systemic circulation, and to decrease side effects and/or ineffectiveness associated with other administration routes. Nowadays different controlled-release technologies are available and can be used for the development of such delivery systems. However, the drug release pattern of the delivery system is critical and must be carefully adapted taking into account the specific physiological features of the oral cavity. Obviously, solid dosage forms are now likely to offer new opportunities in this area. Different strategies have been based on: (a) solely prolonging the duration of the absorption process, (b) developing unidirectional delivery systems, and (c) preparing user-friendly oral mucosal delivery systems. The following different dosage forms are generally a combination of those different strategies.

1. Hollow Fibers

Burnside et al. [27] reported the design of a microporous hollow fiber of polysulfone (molecular weight cutoff was 500,000 Daltons) intended for the delivery of histrelin, an LHRH agonist. This hollow fiber was designed to be placed in the buccal cavity for drug delivery. Preliminary experiments showed that peptide delivery rates could be adjusted and prolonged for up to 6 h. However, the lack

Copyright © 2003 Marcel Dekker, Inc.

of intimate contact with the mucosa may be detrimental to peptide absorption because of possible enzymatic degradation in the saliva.

2. Bioadhesive Tablets

In recent years the development of bioadhesive drug delivery systems intended for oral mucosal drug administration has been the subject of intensive research. Design of immobilized systems is rather sophisticated because it is necessary to impart two specific properties to the system, i.e., immobilization and controlled-release characteristics. Such a combination of different properties within a single system can be achieved by the use of polymers. Immobilization can be achieved by bioadhesion or mucoadhesion, using specifically bioadhesive polymers.

Bioadhesive tablets are immobilized drug delivery systems, which consist of either monolithic, partially coated, or multilayered matrices [28,29], according to different spatial arrangements, which are detailed in Figure 2. Monolithic tablets are easy to manufacture by conventional techniques. They provide the possibility of holding large amounts of drug. Drugs can be coformulated with an absorption enhancer if required. A partial coating of monolithic tablets has been proposed, consisting of protection of every face of the tablet that is not in contact with the mucosa. Such systems allow unidirectional drug release (Fig. 2) and avoid drug dispersion in saliva fluids. Multilayered tablets permit a variety of geometric arrangements. In the case of bilayered tablets, drug release can be rendered almost undirectional. The drug can be incorporated in the adhesive layer in front of the mucosal surface and protected from the oral cavity environment by an upper inert layer. Alternatively, the drug can be incorporated in the upper nonadhesive layer. In this case, drug delivery occurs into the whole oral cavity.

Much attention has been paid to the adhesive characteristics of tablets [30–41]. The use of cellulosic ethers, acrylic polymers, chitosan, sodium alginate, or high-molecular-weight polyoxyethylene generally offers almost immediate, high-adhesion performance for prolonged periods of time, even when drug content is high. Factors influencing drug release from bioadhesive tablets are the same as those encountered in hydrophilic matrices, including the nature of the polymer, the drug/polymer ratio, and the swelling kinetics of the system. Various drugs intended for systemic activity have been incorporated in bioadhesive oral mucosal tablets, including propranolol [38,39], timolol [40], metronidazole [34], metoclopramide [41], insulin [42], nitroglycerine [43], codeine [30], morphine sulfate [44], diltiazem [45], omeprazole [46,47], chlorepheniramine maleate [48], and metoprolol tartrate [49].

Bioadhesive tablets have demonstrated interesting performance. For example, Miyazaki et al. [45] reported that absorption of diltiazem, a calcium channel blocker, could be considerably enhanced by using bioadhesive tablets based on

Copyright © 2003 Marcel Dekker, Inc.

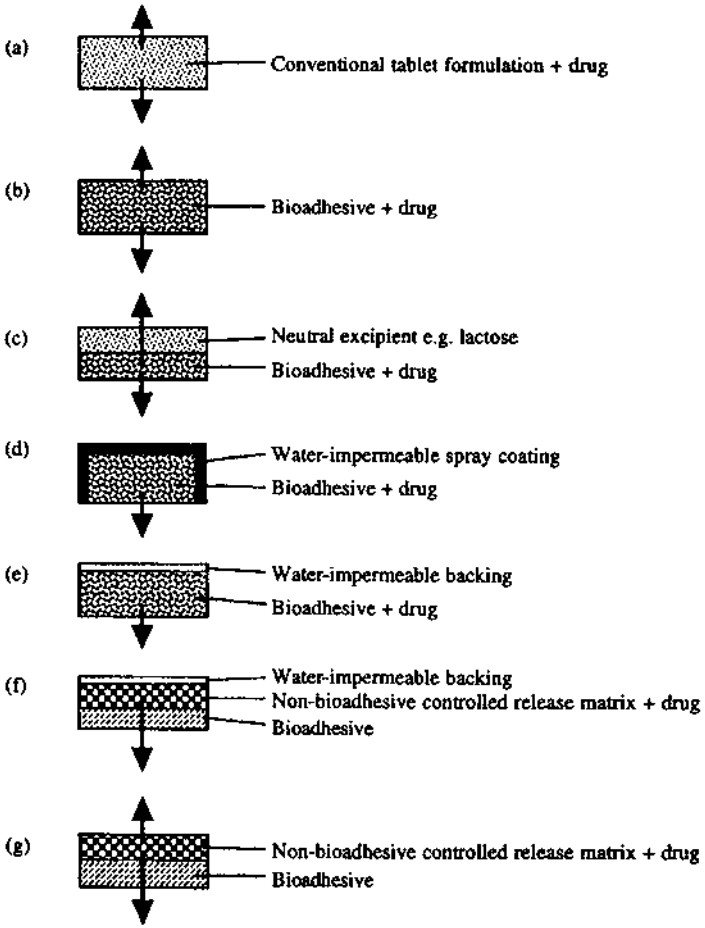


Figure 2 Schematic representation of possible designs of solid oral mucosal drug delivery systems for systemic drug delivery [29].

chitosan and sodium alginate. The bioavailability of diltiazem in rabbits was 69.6% from tablets compared with 30.4% by oral administration. The buccal bioavailability of omeprazole in hamsters was 13.7%, suggesting the potential for this dosage form [47].

The limitations of adhesive tablets include the small surface of contact with the mucosa and their lack of flexibility. High drug release rates, which can be required for some drugs, are difficult to achieve. Finally, the extent and frequency

Copyright © 2003 Marcel Dekker, Inc.

of contact, which might cause irritation following chronic application of those systems on the buccal or sublingual mucosa, have not been fully investigated.

3. Laminated Systems and Patches

In response to some of the drawbacks of tablets, different flexible, high-surface-area, adhesive films and laminated adhesive patches have been investigated for oral mucosal drug delivery.

Different polymers can be used for the development of mucosal patches, including cellulose derivatives (e.g., methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose), natural gums (guar gum, Karaya gum, agarose), and polyacrylates, including poly(acrylic acid), poly(methacrylic acid), poly(vinylpyrrolidone), poly(ethylene glycol), and gelatin. These polymers exhibit mucoadhesive properties and form adhesive hydrogels in the presence of saliva.

Drug-loaded adhesive films can be prepared quite easily by using adhesive polymers. Kurosaki et al. [50] reported the use of a simple film of hydroxypropylcellulose for the delivery of propranolol. Rodu et al. [51] prepared a simple film by complexing hydroxypropylcellulose with tannic and boric acid (Zilactin®).

Adhesive patches can be designed either for unidirectional release into the oral mucosa or for bidirectional release into the mucosa as well as into the oral cavity [52]. The adhesive part of the system can be used as a drug carrier or as a simple adhesive for the retention of a drug-loaded nonadhesive layer on the mucosa. In this respect, a peripheral adhesive ring is feasible. The use of an impermeable backing layer will maximize the drug concentration gradient and prolong adhesion because the system is protected from saliva. Typically the size of such systems can be 1–3 cm^2 but can be up to 10–15 cm^2 depending on the site of administration. Poly(acrylic acid)-based patches have been used successfully for the delivery of opioid analgesics. Bioavailability in dogs ranged from 35% to 50%, compared to oral bioavailability, which was less than 5% [53]. Veillard et al. [54] developed a patch in conjunction with 3M-Riker consisting of a rate-limiting membrane, a polycarbophil adhesive layer, and an impermeable backing. Finally, Merkle et al. [52,55,56] investigated a number of polymers and different geometries for the design of patches for the delivery of different peptides, such as protirelin and octreotide. Studies on octreotide illustrate some of the drawbacks of such systems. Relative bioavailabilities of octreotide in rats of different patches ranged between 17% and 24% when compared to buccal administration of an aqueous solution. Such a result suggests that retardation in the drug release occurred because of insufficient diffusion of the drug through the adhesive layer. Such a phenomenon is not likely to favor drug absorption of such products. Therefore, a recent trend consists of the combination of a fast-

Copyright © 2003 Marcel Dekker, Inc.

dissolving unit and a bioadhesive portion in the same controlled-delivery system [57].

VIII. CONCLUSIONS

The oral cavity is a challenging route for drug delivery. Three main challenges need to be overcome. These include permeability enhancement, dosage form retention at the site of application, and the continuous secretion of saliva and its subsequent swallowing, which can lead to substantial drug loss from the dosage form and hence low bioavailability. However, despite this, much interest has been expressed in exploiting the oral cavity as a portal for the delivery of drugs to the systemic circulation.

The historical approaches taken to develop drug delivery systems for use in the oral cavity have been outlined here. The following chapters introduce some of the more recent approaches that have been taken to design dosage forms and delivery systems for oral mucosal drug delivery. In contrast to the chapters in the other parts of this book, the following chapters comprise a mixture of commercially available and conceptual delivery systems. This is a reflection of the challenges that are associated with this route for drug delivery that have limited the number of commercially available technologies for this route for drug delivery.

REFERENCES

1. CA Lesch, CA Squier, AH Cruchley, DM Williams, PM Speight. The permeability of human oral mucosa and skin to water. J Dent Res 68:1345–1349, 1989.
2. HE Schroeder. Differentiation of Human Oral Stratified Epithelium. Basel: S Karger, 1981, p. 33.
3. CA Squier, NW Johnson, RM Hopps. Human Oral Mucosa: Development, Structure and Function. Oxford: Blackwell Scientific, 1976.
4. LMC Collins, C Dawes. The surface area of the adult human mouth and the thickness of the salivary film covering the teeth and oral mucosa. J Dent Res 66:1300–1302, 1987.
5. CA Squier. Membrane coating granules in nonkeratinized oral epithelium. J Ultrastruct Res 60:212–220, 1977.
6. AF Hayward. Membrane coating granules. Int Rev Cytol 59:97–127, 1979.
7. PW Wertz, DC Swartzendruber, CA Squier. Regional variation in the structure and permeability of oral mucosa and skin. Adv Drug Del Rev 12:1–12, 1993.
8. PB Innes. The nature of granules within sulcular epithelial cells. J Periodont Res 8: 252–262, 1973.

Copyright © 2003 Marcel Dekker, Inc.

9. S Silverman Jr. Nonkeratinization and keratinization: the extremes of the human range. In: CA Squier, J Meyer, eds. Current Concepts of the Histology of Oral Mucosa. Springfield, IL: Charles C Thomas, 1971.
10. AF Hayward. Electron microscopic observations on cell coat and membrane-coating granules of the epithelium of the hard and soft palate in the rat. Arch Oral Biol 18: 67–75, 1973.
11. CA Squier, PW Wertz, P Cox. Thin-layer chromatographic analysis of lipids in different layers of porcine epidermis and oral epithelium. Arch Oral Biol 36:647–653, 1991.
12. WM Edgar. Saliva: its secretion, composition and functions. Br Dent J 172:305–312, 1992.
13. ID Mandel, S Wotman. The salivary secretions in health and disease. Oral Sci Rev 8:25–47, 1976.
14. LA Tabak, MJ Levine, ID Mandel, SA Ellison. Role of salivary mucins in the protection of the oral cavity. J Oral Pathol 11:1–17, 1982.
15. I Lindqvist, KB Augustinsson. Esterases in human saliva. Enzyme 20:277–291, 1975.
16. LB Hansen, LL Christup, H Bundgaard. Saliva-catalysed hydrolysis of a ketobemidone ester: factors influencing human salivary esterase activity. Int J Pharm 88:221–227, 1991.
17. LB Hansen, LL Christup, H Bundgaard. Ketobemidone prodrugs for buccal delivery: prediction of the extent of saliva-catalysed hydrolysis of various ester prodrugs under simulated in vivo conditions. Int J Pharm 88:229–235, 1992.
18. CA Squier. The permeability of keratinized and non-keratinized oral epithelium to horseradish peroxidase. J Ultrastruct Res 43:160–177, 1973.
19. CA Squier, L Rooney. The permeability of keratinized and non-keratinized oral epithelium to lanthanum in vivo. J Ultrastruct Res 54:286–295, 1976.
20. G Ponchel. Formulation of oral mucosal drug delivery systems for the systemic delivery of bioactive materials. Adv Drug Del Rev 13:75–87, 1994.
21. A Sobrero. Sur plusieurs composés détonnants produits avec l'acide nitrique et le sucre, la dextrine, la lactine, la mannite et la glycérine. Compt Rend Hebdomad Séances Acad Sci 24:247–248, 1847.
22. TH Stanley, MA Ashburn. Novel delivery systems: oral transmucosal and intranasal transmucosal. J Pain Sympt Manage 7:163–171, 1992.
23. M Lagas, AMJA Duchateau. Sublingual nitroglycerin. I. Comparative evaluation of the physical stability of commercially available tablets. Pharmaceutisch Weekblad Sci Ed 10:246–253, 1988.
24. M Lagas, AMJA Duchateau. Sublingual nitroglycerin. II. In vitro and in vivo availability of Nitrostat and Nitrobaat tablets. Pharmaceutisch Weekblad Sci Ed 10:254–258, 1988.
25. DH Maddox, BA Burnside, AD Keith. Buccal delivery of progesterone. Proc Int Symp Control Rel Bioact Mater 17:291–292, 1990.
26. CG Wilson, N Washington, J Peach, GR Murray. J Kennerley. The behaviour of a fast-dissolving dosage form (Expidet) followed by γ-scintigraphy. Int J Pharm 40: 119–123, 1987.
27. BA Burnside, AD Keith, W Snipes. Microporous hollow fibers as a peptide delivery

Copyright © 2003 Marcel Dekker, Inc.

system via the buccal cavity. Proc Int Symp Control Rel Bioact Mater 16:93–94, 1989.
28. G Ponchel, D Duchêne. Development of a bioadhesive tablet. In M Szycher, ed. High Performance Biomaterials: A Comprehensive Guide to Medical and Pharmaceutical Applications. Lancaster: Technomic, 1992, pp. 231–242.
29. MJ Rathbone, G Ponchel, F Ghazali. Systemic oral mucosal drug delivery and delivery systems. In: MJ Rathbone, ed. Oral Mucosal Drug Delivery. New York: Marcel Dekker, 1996, pp. 241–284.
30. KV Ranga Rao, A Ben-Amor, P Buri. Studies on buccoadhesive tablet formulation of codeine phosphate. STP Pharma 5:899–903, 1989.
31. Y Jacques, D Chulia, A Verain, P Ozil. A propos d'un comprimé mucoadhésif destiné à la cavité buccale. Pharm Acta Helv 64:163–167, 1989.
32. G Ponchel, F Touchard, D Duchêne, NA Peppas. Bioadhesive analysis of controlled-release systems. I. Fracture and interpenetration analysis in poly(acrylic acid)-containing systems. J Control Rel 5:129–141, 1987.
33. NA Peppas, G Ponchel, D Duchêne. Bioadhesive analysis of controlled-release systems. II. Time-dependent bioadhesive stress in poly(acrylic acid)-containing systems. J Control Rel 5:143–149, 1987.
34. G Ponchel, F Touchard, D Wouessidjewe, D Duchêne, NA Peppas. Bioadhesive analysis of controlled-release systems. III. Bioadhesive and release behavior of metronidazole-containing poly(acrylic acid)-hydroxypropyl methylcellulose systems. Int J Pharm 38:65–70, 1987.
35. F Lejoyeux, G Ponchel, D Duchêne. Influence of some technological parameters on the bioadhesive characteristics of poly(acrylic acid) matrices. STP Pharma 5:893–898, 1989.
36. JD Smart. An evaluation of some mucosa-adhesive dosage forms for drug delivery to the oral cavity. J Pharm Pharmacol 42:141P. 1990.
37. P Forget, P Gazzeri, F Moreau, M Sabatier, C Durandeau, JP Merlet, P Aumonier. Comprimés mucoadhésifs: mesure de l'adhésivité in vitro. STP Pharma 4:176–181, 1988.
38. WG Chen, GC-C Hwang. Adhesive and in vitro characteristics of propranolol bioadhesive disc system. Int J Pharm 82:61–66, 1992.
39. O Kislal, N Celebi. Studies on bioadhesive tablet formulation of propranolol HCl. Proc Int Symp Control Rel Bioact Mater 19:397–398, 1992.
40. PB Deasy, CT O'Neill. Bioadhesive dosage form for peroral administration of timolol base. Pharm Acta Helv 64:231–235, 1989.
41. N Garcia-Gonzalez, H Blanco-Fuente, S Anguiano-Igea, B Delgado-Charro, FJ Otero-Espinar, J Blanco-Méndez. In vitro characterization of bioadhesive metoclopramide tablets for buccal application prepared with polyacrylic acid and hydroxypropyl methylcellulose. STP Pharma Sci 2:494–499, 1992.
42. T Nagai, R Konishi. Buccal/gingival drug delivery systems. J Control Rel 6:353–360, 1987.
43. JM Schor, SS Davis, A Nigalaye, S Bolton. Susadrin transmucosal tablets. Drug Dev Ind Pharm 9:1359–1377, 1983.
44. S Anlar, Y Capan, AA Hincal. Studies on buccoadhesive tablet formulation of morphine sulfate. 6th Int Conf Technol Pharm, Paris, 2–4 June. 1992, pp. 30–39.

Copyright © 2003 Marcel Dekker, Inc.

45. S Miyazaki, A Nakayama, M Oda, M Takada, D Attwood. Drug release from oral mucosal adhesive tablets of chitosan and sodium alginate. Int J Pharm 118:257–263, 1995.
46. H-G Choi, C-K Kim. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. J Control Rel 68:397–404, 2000.
47. H-G Choi., J-H Jung, CS Yong, C-D Rhee, M-K Lee, J-H Han, K-M Park, C-K Kim. Formulation and in vivo evaluation of omeprazole buccal adhesive tablets. J Control Rel 68:405–412, 2000.
48. HH Alur, SI Pather, AK Mitra, P Johnston. Transmucosal sustained delivery of chlorpheniramine maleate in rabbits using a novel, natural mucoadhesive gum as an excipient in buccal tablets. Int J Pharm 188:1–10, 1999.
49. D Tiwari, D Goldman, C Town, R Sause, PL Madan. In vitro–in vivo evaluation of a controlled release buccal bioadhesive device for oral drug delivery. Pharm Res 16:1775–1780, 1999.
50. Y Kurosaki, T Takatori, M Kitayama, T Nakayama, T Kimura. Application of propranolol to the keratinized oral mucosa: avoidance of first-pass elimination and the use of 1-dodecylazacycloheptan-2-one (Azone) as an absorption enhancer of bioadhesive film-dosage form. J Pharmacobio-Dyn 11:824–832, 1988.
51. B Rodu, CM Russell, AJ Desmarais. Clinical and chemical properties of a novel mucosal bioadhesive agent. J Oral Pathol 17:564–567, 1988.
52. HP Merkle, GJM Wolany. Muco-adhesive patches for buccal peptide administration. In: Minutes European Symposium on Buccal and Nasal Administration as an Alternative to Parenteral Administration. Paris: Editions de Santé, 1992, pp. 116–124.
53. MA Hussain, BJ Aungst, CA Koval, E Shefter. Improved buccal delivery of opioids, analgesics, and antagonists with bitterless prodrugs. Pharm Res 5:615–618, 1988.
54. MM Veillard, MA Longer, TW Martens, JR Robinson. Preliminary studies of oral mucosal delivery of peptide drugs. J Control Rel 6:123–131, 1987.
55. R Anders, HP Merkle. Evaluation of laminated mucoadhesive patches for buccal drug delivery. Int J Pharm 49:231–240, 1989.
56. HP Merkle, G Wolany. Buccal delivery of peptide drugs. J Control Rel 21:155–164, 1992.
57. Y Nozaki, M Kakumoto, M Ohta, K Yukimatsu, Y Chien. A new transmucosal therapeutic system: overview of formulation development and in vitro/in vivo clinical performance. Drug Dev Ind Pharm 19:221–275, 1993.

Copyright © 2003 Marcel Dekker, Inc.

30

Slowly Disintegrating Buccal Mucoadhesive Plain-Tablet (S-DBMP-T) and Buccal Covered-Tablet System (BCTS)

Katsumi Iga
Takeda Chemical Industry Ltd., Osaka, Japan

I. INTRODUCTION

Drugs that are administered via the buccal mucosa directly enter the systemic circulation, thereby avoiding hepatic first-pass metabolism. Therefore, this administration route is useful for improving the bioavailability of drugs that are subject to an extensive first-pass effect when delivered orally.

For the oral mucosal route of drug administration, various types of dosage forms can be prepared. A sublingual tablet can afford rapid drug absorption and a prompt pharmacological effect; however, the duration of delivery is short owing to the inevitable loss of a large proportion of the administered dose due to swallowing. To avoid such losses, a patch can be formulated that is located on the buccal mucosa of the oral cavity. However, this approach is limited by the thicker dimensions of the buccal membrane compared to the others that line the oral cavity, and constraints impelled by the delivery system itself (the amount of drug reaching the systemic circulation is limited by the area of the mucosa that the patch covers, which, for patient comfort reasons, is relatively small). Our research [1,2] has demonstrated that an appropriately formulated, slowly disintegrating tablet whose shape, dimensions, and formulation enable it to be placed on the gingival surface both avoids absorption losses due to swallowing and releases its contents over a wide area of the buccal cavity thereby promoting absorption

Copyright © 2003 Marcel Dekker, Inc.

and affording a sustained delivery. We have shown that gingival administration to dogs of propranolol (as the free base) and lidocaine (as the free base) formulated in the slowly disintegrating buccal mucoadhesive plain-tablet (S-DBMP-T) achieves almost complete bioavailability, which contrasts markedly to the low oral bioavailability of these compounds [1,2].

The S-DBMP-T system is a simple approach. However, over extended periods of administration the system was observed to soften and lose its shape due to mouth movement, which hindered control of the disintegration of the tablet over long administration periods. For that reason, we developed a second technology, which is essentially an extension of the S-DBMP-T system. The improved technology involved covering the S-DBMP-T system with a polyethylene film that had a hole in it. We refer to this technology as the buccal covered-tablet system (BCTS) and have demonstrated that this technology can prolong the duration of absorption of glyceryl trinitrate and isosorbide dinitrate [3,4].

The S-DBMP-T and BCTS systems are described in this chapter.

II. S-DBMP-T

A. Formulation and Preparation

S-DBMP-T are prepared by incorporating a relatively large amount of hydroxypropylcellulose in a tablet formulation. An example of a typical composition is a tablet composed of 20 mg of drug, 20 mg of hydroxypropylcellulose, 20 mg of carboxymethylcellulose (ECG-505, disintegrating agent), and 60 mg of lactose. These components are mixed, and then compressed into a tablet with a flat-faced die that is 8 mm in diameter.

B. In Vivo Studies

1. Human Studies

Studies in humans that involved placing the tablet formulation (containing no drug) onto the gingiva showed that sufficient adhesiveness to the gingiva as well as slow-disintegration characteristics were obtained in humans when the tablet was stuck at a site of the upper gingiva (note that in the study prior to administration, moisture was removed from the gingiva by wiping with tissue paper) (Fig. 1) [1].

2. Canine Studies

To examine the oral mucosal absorption of drugs formulated into the S-DBMP-T technology, beagle dogs were used as experimental animals. For this animal, however, the adhesiveness of the tablet to the gingiva was not adequate. There-

Copyright © 2003 Marcel Dekker, Inc.

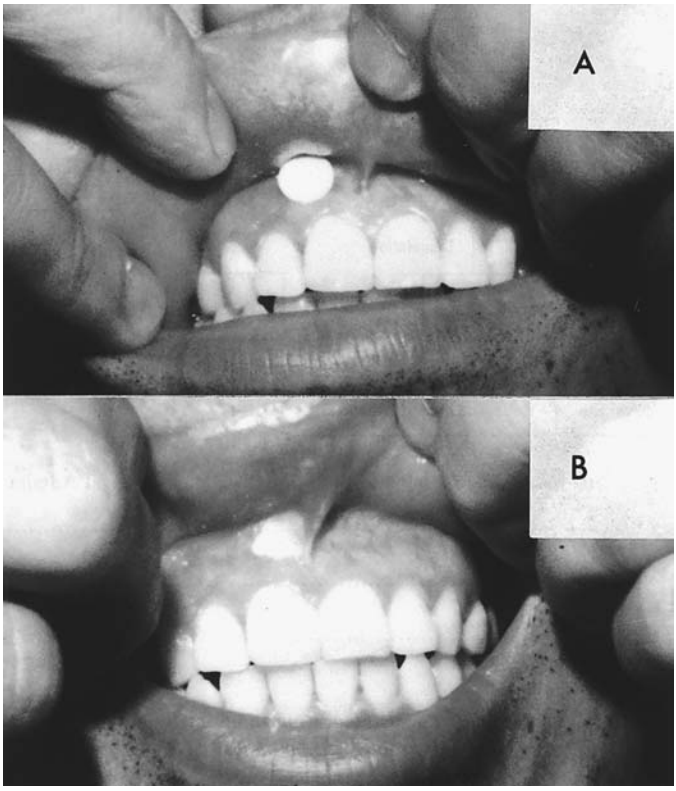


Figure 1 A buccal plain-tablet administered on the gingiva in a human: (A) immediately after administration; (B) 2 h after administration. (Reproduced from Ref. [1].)

fore, to help the tablet adhere to the upper gingiva, about 10 mg of carbopol 941 powder (cross-linked acrylic acid polymer) was placed onto the bottom of the tablet immediately prior to administration [1].

The S-DBMP-T technology was originally developed for increasing the bioavailability of oxendolone (a steroidal antiandrogen). This compound undergoes rapid presystemic elimination when administered orally. It should be noted that the presystemic elimination of oxendolone is unlike that of propranolol, which also undergoes rapid presystemic elimination. Figure 2 shows the blood drug levels after intravenous and oral administration of oxendolone and propranolol to dogs. The blood drug levels were observed to rapidly decrease after intravenous administration of both drugs and the blood drug levels after oral administration were very low for both compounds. With propranolol, the oral

Copyright © 2003 Marcel Dekker, Inc.

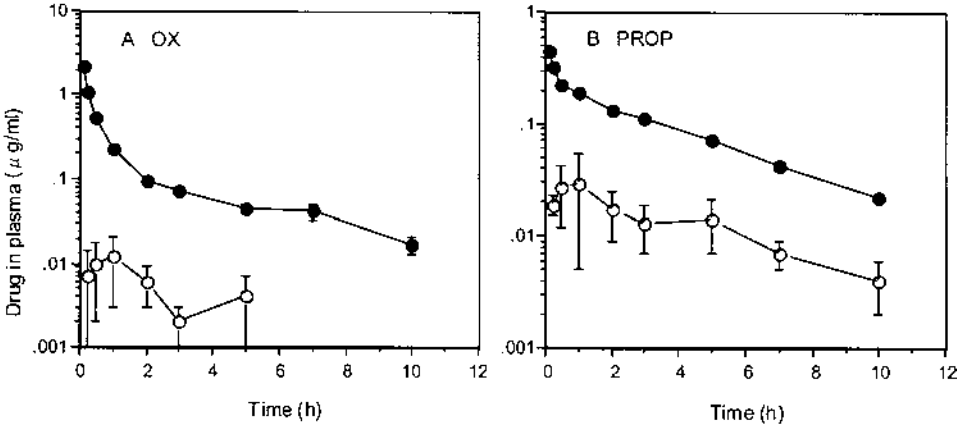


Figure 2 Plasma drug levels after intravenous and oral administration of oxendolone and propranolol to dogs: dose: 20 mg/dog. (Reproduced from Ref. [2].)

bioavailability was 13%. This low oral bioavailability can be explained by rapid drug elimination due to the hepatic first-pass effect. The oral bioavailability of oxendolone was observed to be extremely low (1% at most). In contrast to propranolol, the low bioavailability of oxendolone can be explained by both drug elimination during gastrointestinal absorption and the hepatic first-pass effect [1].

The plasma drug levels after gingival administration of S-DBMP-T, each containing the steroids oxendolone, methyltestosterone, progesterone, and chlormadinone acetate and the nonsteroidal drugs propranolol and chlorpromazine (as the free base), are shown in comparison with the oral administration of these compounds in Figures 3 and 4.

Figures 3 and 4 show that the plasma levels for all drugs delivered using the S-DBMP-T technology were much higher compared to when they were administered orally. The buccal bioavailabilities can be calculated on the same AUC basis as the oral bioavailabilities. However, this bioavailability value includes the bioavailability of any swallowed drug (overall buccal bioavailability). The net buccal bioavailability can be calculated by the following equation:

$$BA_{buc(overall)} = BA_{buc(net)} + [1 - 1/100 \cdot BA_{buc(net)}] \cdot BA_{oral} \quad (1)$$

where $BA_{buc(overall)}$, $BA_{buc(net)}$, and BA_{oral} refer to the overall buccal bioavailability, the net buccal bioavailability, and the oral bioavailability, respectively. The $BA_{buc(overall)}$ and $BA_{buc(net)}$ as well as BA_{oral} of these drugs are listed together with their physicochemical properties and in vitro first-order buccal absorption rates in Table 1.

Copyright © 2003 Marcel Dekker, Inc.

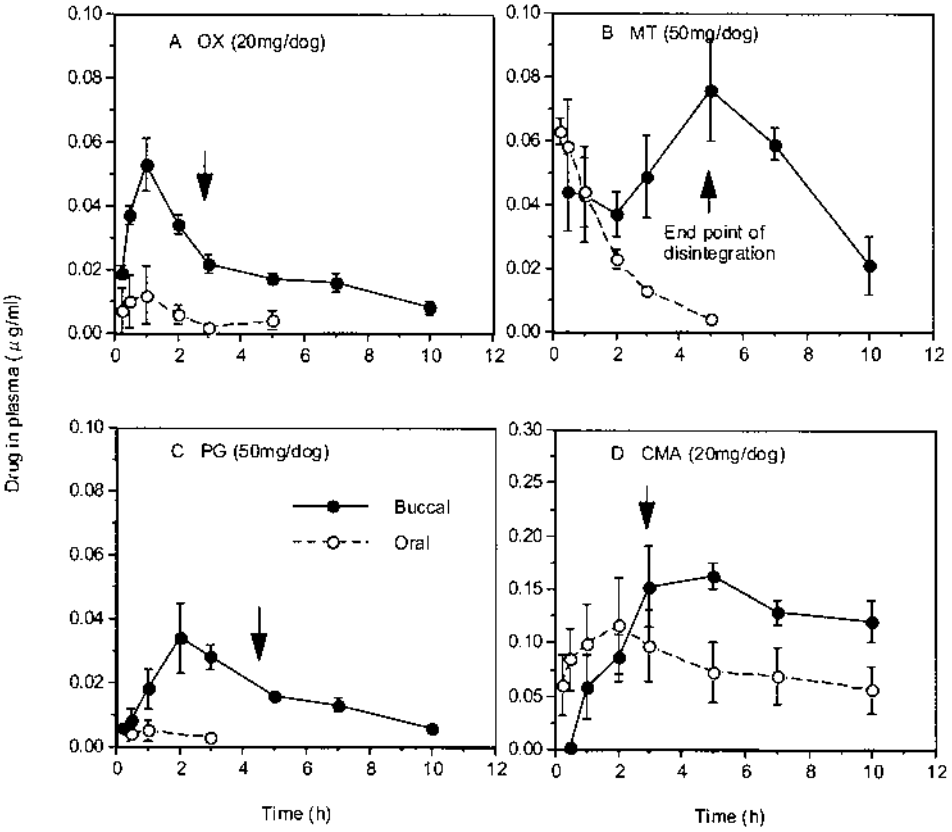


Figure 3 Plasma drug levels after gingival administration of buccal plain-tablets each containing presystemically eliminating steroids (oxendolone, methyltestosterone, progesterone, and chlormadinone acetate) in comparison with oral administration: dose: oxendolone, chlormadinone acetate: 20 mg/dog; methyltestosterone, progesterone: 50 mg/dog. (Reproduced from Ref. [2].)

The $BA_{buc(net)}$ of chlormadinone acetate and chlorpromazine accounted for 47% and 75% of the overall bioavailability, respectively, while the $BA_{buc(net)}$ of the other drugs comprised more than 90% of the overall bioavailability. These results indicate that the increase in bioavailability is mostly attributable to the avoidance of hepatic first-pass elimination.

With propranolol, the $BA_{buc(net)}$ for S-DBMP-T was shown to be 92%, which indicates almost all the drug was absorbed. This contrasts markedly to the low oral bioavailability. The $BA_{buc(net)}$ for the relatively fast-disintegrating tablet

Copyright © 2003 Marcel Dekker, Inc.

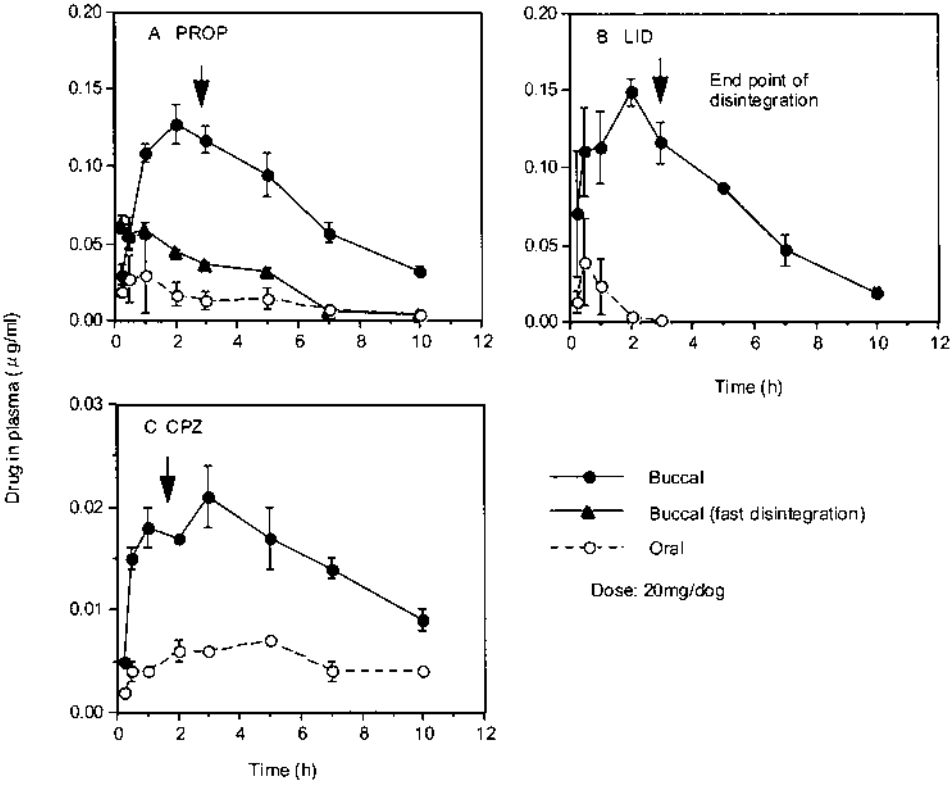


Figure 4 Plasma drug levels after gingival administration of buccal plain-tablets each containing presystemically eliminating nonsteroidal drugs (propranolol; lidocaine; chlorpromazine) in comparison with oral administration: dose: 20 mg/dog. (Reproduced from Ref. [2].)

whose disintegration time was 20 min resulted in a $BA_{buc(net)}$ of 31%, indicating absorption losses through swallowing. Similar data with oxendolone have been reported that showed that tablets exhibiting disintegration times shorter than 1 h (10 or 45 min) gave high plasma levels at early times, but did not show a large increase in $BA_{buc(net)}$, while tablets exhibiting a longer disintegration time (3 or 5 h) showed relatively high plasma levels until the end of disintegration and a plateau level of $BA_{buc(net)}$ (around 20%). For this reason, slow disintegration of a tablet is important to minimize losses and to achieve high $BA_{buc(net)}$.

It is interesting to note that propranolol and lidocaine both showed almost complete absorption when administered in the S-DBMP-T system, while the other

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Oral and Buccal Bioavailabilities of Presystemically Eliminated Drugs, in Comparison with Their Physicochemical Properties and In Vitro First-Order Buccal Absorption Rates

Drug	BA_{oral} (%)	$BA_{buc(overall)}$ (%)	$BA_{buc(net)}$ (%)	C_s (mg/mL)	pK_a	log P[a]	$K_{ab(in\ vitro)}$[b] (L/min)
Oxendolone	<1	22	22	0.01		4.0	0.077
Methyltestosterone	10	56	46	0.04		3.3	0.042
Progesterone	<1	47	47	0.01		4.0	0.083
Chlormadinone acetate	24	38	18	0.002		>4.0	0.12
Propranolol	13	93	92	0.39[c]	9.5	3.5	0.11
Lidocaine	6	100	97	3.44[c]	7.8	1.6	0.037
Chlorpromazine	12	37	28	ND	9.2	5.3	0.16

[a] Between *n*-octanol and water.

[b] In vitro first-order buccal absorption rate; from the initial slope of the drug-solution-concentration-time curve obtained by the incubation of an isolated rat tongue with a drug solution (pH 9.6).

[c] pH 9.6.

Source: Reproduced from the data in Ref. [2].

Copyright © 2003 Marcel Dekker, Inc.

drugs studied showed incomplete buccal absorption. Propranolol and lidocaine both exhibit relatively high aqueous solubility, whereas the remaining compounds exhibit low aqueous solubility (Table 1). This suggests that buccal delivery from the S-DBMP-T system depends largely on the drug's aqueous solubility. This observation helps define the physicochemical characteristics of drugs that are suitable for inclusion in the S-DBMP-T system.

C. Factors Determining Bioavailability of Buccal Tablet

To gain a better understanding of how aqueous solubility and buccal absorption rate determine $BA_{buc(net)}$, buccal absorption after gingival administration of a buccal tablet was analyzed by a compartmental model based on the first-order rate kinetics as shown in Figure 5.

Compartment 1 represents a buccal tablet on the gingival surface that will be disintegrated into solid drug particles and be distributed throughout the buccal cavity; compartment 2 represents the solid drug particles distributed over the buccal cavity that will be dissolved in the saliva or swallowed without dissolution; compartment 3 represents the dissolved drug that will be absorbed by the buccal mucosal membrane and enter the systemic circulation or will be swallowed with-

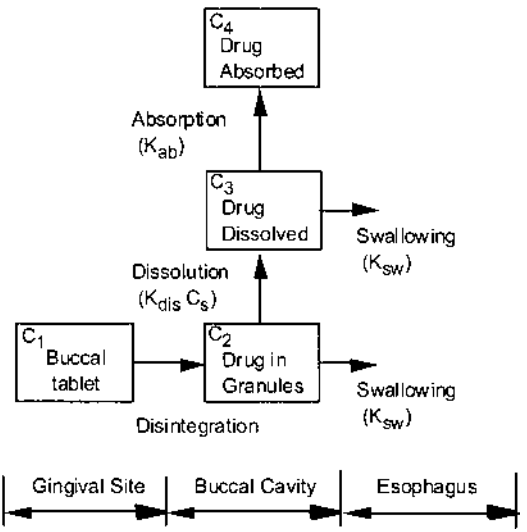


Figure 5 Kinetic model for buccal drug absorption after gingival administration of a buccal tablet. (Reproduced from Ref. [2].)

Copyright © 2003 Marcel Dekker, Inc.

out absorption; and compartment 4 represents the drug absorbed into the systemic circulation (K_{ab} and K_{sw} represent first-order rates for drug absorption rate and drug-swallowing rate, respectively).

From this model, simultaneous differential equations that express first-order rate kinetics can be set up (not shown). Then, if disintegration of the tablet is slow enough to allow the assumption that the drug concentration in the saliva is far lower than the aqueous drug solubility (C_s)($C \ll C_s$: sink condition) (this assumption is valid in light of the kinetic analysis of the relationship between $BA_{buc(net)}$ of oxendolone and disintegration time) [1], the drug dissolution rate can be approximately described by a first-order rate constant ($K_{dis}C_s$) where K_{dis} represents a dissolution rate constant relating to the surface area and the diffusion constant (mL/mg/h), and thus, the $BA_{buc(net)}$ can be expressed as:

$$BA_{buc(net)} = 100 \cdot K_{ab}/(K_{ab} + K_{sw})\, K_{dis}C_s/(K_{dis}C_s + K_{sw}) \quad (2)$$

If $K_{ab} \gg K_{sw}$ in Eq. (2), then

$$BA_{buc(net)} = 100 \cdot K_{dis}C_s/(K_{dis}C_s/(K_{dis}C_s + K_{sw}) \quad (3)$$

IF $K_{dis}C_s \gg K_{sw}$ in Eq. (2), then

$$BA_{buc(net)} = 100 \cdot K_{ab}/(K_{ab} + K_{sw}) \quad (4)$$

The value for K_{sw} has been determined by measuring the amount of Yellow-5 (nonabsorbed dye) remaining in the mouth after buccal administration of Yellow-5-containing granules (20 mg) in humans and the value estimated from the plots of the remaining amount versus time was 6/h [1]. This value was consistent with that estimated from the reported salivary flow rate in humans [5] by assuming the volume of the buccal fluid to be 1 mL.

The K_{ab} value for propranolol can be estimated to be around 3000/h from the reported data [6], and the K_{ab} for lidocaine can be estimated to be around 1000/h from the data that log P or $K_{ab(invtro)}$ for lidocaine is about one-third that for propranolol (Table 1). These values are far larger than the swallowing rate. Thus the $BA_{buc(net)}$ for the drugs tested by Iga et al. can be predicted by Eq. (3). By assuming $K_{dis} = 150$ mL/mg/h (based on the result of the kinetic analysis of the relationship between $BA_{buc(net)}$ of oxendolone and disintegration time) [1], and $K_{sw} = 6$/h, then $BA_{buc(net)} = 100 \times 150C_s/(150C_s + 6)$. Plots of the experimentally obtained $BA_{buc(net)}$ versus the $BA_{buc(net)}$ obtained from these calculations resulted in a fairly good agreement between the experimental results and theory (Fig. 6).

According to the above theory, if a drug exhibits lipophilicity high enough to assume $K_{ab} \gg K_{sw}$ (the C_s is probably low because of the high lipophilicity), then the $BA_{buc(net)}$ is determined by Eq. (3). By assuming $K_{sw} = 6$/h, $BA_{buc(net)} = 100 \cdot K_{dis}C_s/(K_{dis}C_s + 6)$. A C_s of 0.04 mg/mL, such as that for methyltestoster-

Copyright © 2003 Marcel Dekker, Inc.

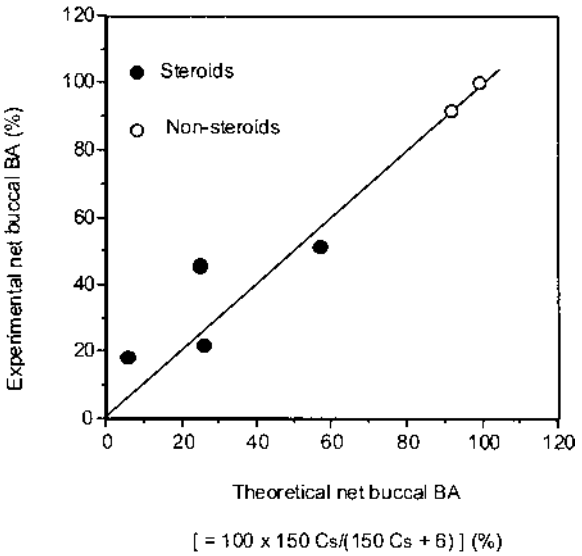


Figure 6 Plots of experimental versus theoretical buccal bioavailability. (Reproduced from Ref. [2].)

one, may act as a reference standard to allow comparison of the $BA_{buc(net)}$ between drugs exhibiting different C_s. For instance, if C_s is 4 times higher, the $BA_{buc(net)}$ is calculated to be 80%.

If a drug exhibits C_s high enough to assume $K_{dis}C_s \gg K_{sw}$ (K_{ab} is probably low because of the low lipophilicity), then the $BA_{buc(net)}$ is determined by $BA_{buc(net)} = 100 \cdot K_{ab}/(K_{ab} + 6)$. According to this equation, a K_{ab} of 3/h results in a $BA_{buc(net)}$ of 33%. This value corresponds to a K_{ab} one-thousandth that for propranolol (Table 1) and a log P smaller than that for propranolol by a factor of 3.0 (log P = 0.5). Thus, a log P of this magnitude may be a minimal requirement for buccal drug absorption.

Peptides may fall into this category. The buccal absorption of peptides has been reported to be increased by using absorption enhancers. According to the present theory, however, K_{ab} is proportional to the reciprocal of the volume of the saliva (V_s; about 1 mL in humans) [5]; therefore, avoidance of increase in V_s may be a way to obtain a large value for K_{ab} of such drugs. For this reason, a buccal tablet, a sheet, or a dry-powder system that can provide a high drug concentration at the absorption site without increasing V_s may be a more suitable formulation than a solution.

Copyright © 2003 Marcel Dekker, Inc.

III. BCTS

A. Limitation of S-DBMP-T System

In addition to the drugs described in the previous section, Iga et al. also examined the buccal absorption of glyceryl trinitrate and isosorbide dinitrate using the S-DBMP-T system. Glyceryl trinitrate and isosorbide dinitrate are both known to undergo extensive first-pass metabolism when administered orally. Iga et al. considered that incorporating these compounds into the S-DBMP-T system would result in an improvement in their bioavailability and achieve a longer duration of action while reducing side effects [7,8].

The plasma drug levels after gingival administration of S-DBMP-T containing glyceryl trinitrate and isosorbide dinitrate to dogs are shown in Figure 7. The plasma drug levels are compared with those of a 5-h infusion with the same dose and also oral administration.

The gingival administration resulted in high plasma drug levels. With isosorbide dinitrate (unlike glyceryl trinitrate), a relatively long disintegration time (around 5 h) was achieved so that the plasma drug level profile was similar to that during the 5-h infusion (note that this disintegration time was the maximally achievable one using the S-DBMP-T system). The buccal bioavailabilities of glyceryl trinitrate and isosorbide dinitrate were estimated to be about 178% and 120%, respectively. Although the bioavailability of these compounds exceeded 100%, the obtained bioavailability values suggested that almost all of the administered dose was absorbed buccally. In contrast, the plasma drug levels after oral administration were very low. The oral bioavailabilities of glyceryl trinitrate and isosorbide dinitrate were about 2% and 5%, respectively. This can be attributed to the extensive hepatic first-pass metabolism of these drugs.

The results suggested that incorporation of glyceryl trinitrate and isosorbide dinitrate into the S-DBMP-T system could successfully prolong the delivery of these compounds into the systemic circulation and avoid the extensive hepatic first-pass metabolism that these compounds are prone to. The S-DBMP-T system was shown to be simple and useful for avoiding the first-pass effects and achieving high bioavailability. However, control of the disintegration time over very extended time periods for the purpose of prolonged release may be limited with this technology. Iga et al. have observed that after the S-DBMP-T system has been moistened, it tends to soften. It then tends to lose its shape due to mouth movement. These processes tend to hinder the control of disintegration over long time periods.

B. BCTS

To maintain the tablet shape for as long as possible, Iga et al. developed a method to restrict disintegration from the sides of the tablets. The method involved sand-

Copyright © 2003 Marcel Dekker, Inc.

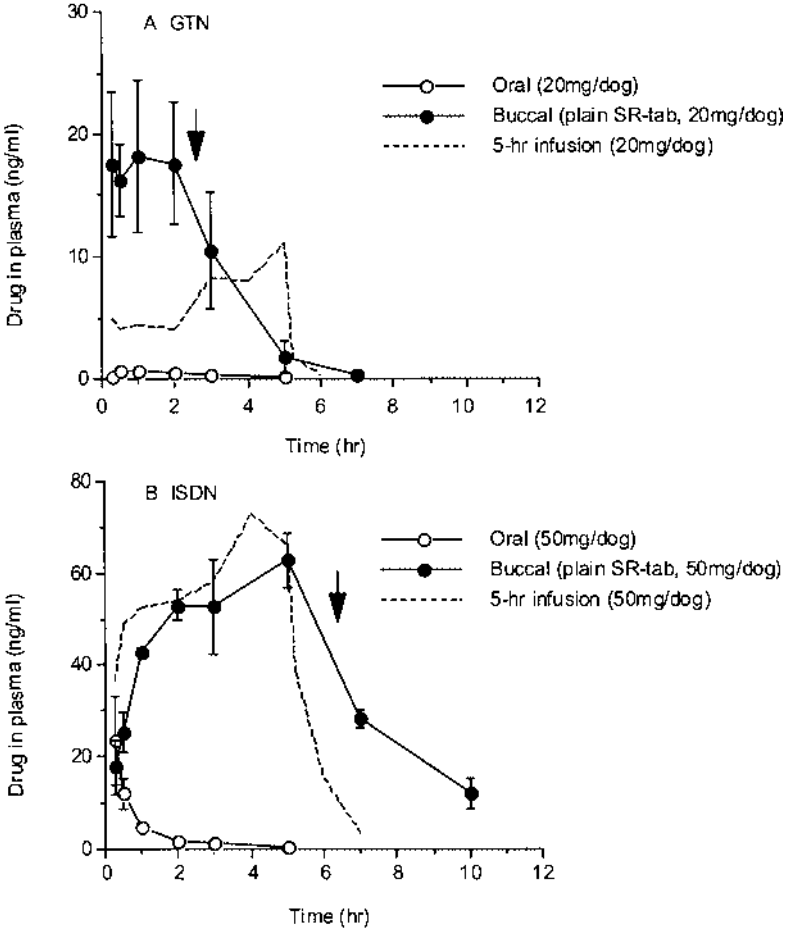


Figure 7 Plasma glyceryl trinitrate and isosorbide dinitrate levels after oral and gingival administration of plain SR-tabs containing glyceryl trinitrate and isosorbide dinitrate to dogs. The arrows indicate the time at which the tablet disintegrated completely and disappeared from the administration site. Plasma drug levels during the 5-h infusion were calculated on the same dose basis using data from the 12.5-mg/dog infusion. (Reproduced from Ref. [4].)

Copyright © 2003 Marcel Dekker, Inc.

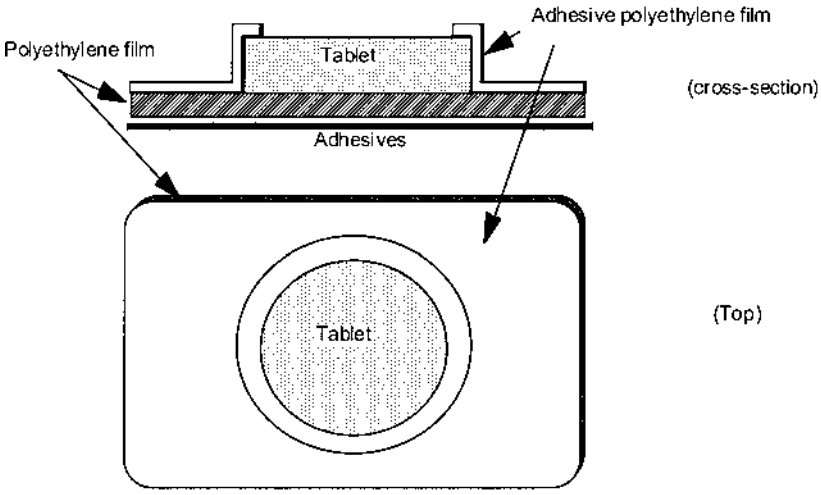


Figure 8 Diagram of covered SR-tab for buccal sustained-release dosage form. (Reproduced from Ref. [4].)

wiching a S-DBMP-T tablet between two polyethylene sheets. The upper sheet contained a hole that allowed the tablet to absorb water and disintegrate only through the hole. The lower sheet contained adhesives to allow the delivery system to adhere to the gingiva for a long time. Iga et al. investigated a hole diameter of 5 mm or 7 mm (when the tablet diameter was 8 mm). A schematic diagram of the system, referred to as BCTS, is shown in Figure 8.

The plasma drug levels in dogs after gingival administration of a BCTS system containing glyceryl trinitrate and isosorbide dinitrate are shown in Figure 9. The dose of both drugs was 5 mg. The dosage form was removed 10 h after administration. With both drugs, the plasma drug level was maintained constant for over 10 h until removal of the dosage form, after which the plasma drug level rapidly decreased. When the BCTS was removed, almost 90% of the tablet had disintegrated and disappeared from between the polyethylene sheets. The bioavailability of glyceryl trinitrate covered tablet was estimated to be 102%.

1. Effect of Hole Diameter

The effect of hole diameter (5 mm or 7 mm) was tested using BCTS systems containing isosorbide dinitrate. The bioavailabilities of the isosorbide dinitrate from BCTS systems with different hole diameters were 89.6% (5 mm) and 86.5% (7 mm), indicating that the drug release occurred independent of hole diameter.

Copyright © 2003 Marcel Dekker, Inc.

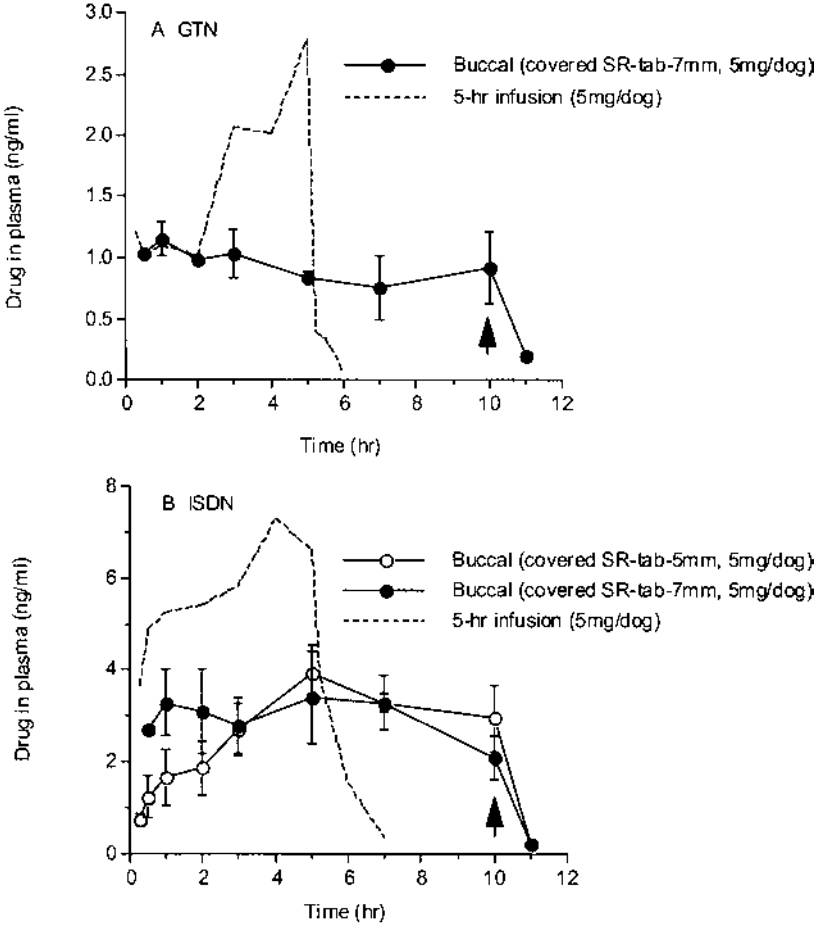


Figure 9 Plasma glyceryl trinitrate and isosorbide dinitrate levels after gingival administration of covered SR-tabs containing glyceryl trinitrate and isosorbide dinitrate to dogs. Covered SR-tab-5mm and covered SR-tab-7mm represent covered SR tablets with a hole 5 and 7 mm in diameter, respectively. The arrows indicate the time at which the dosage form was removed from the administration site. Plasma drug levels for the 5-h infusion were calculated on the same dose basis using data from the 12.5-mg/dog infusion. (Reproduced from Ref [4].)

Copyright © 2003 Marcel Dekker, Inc.

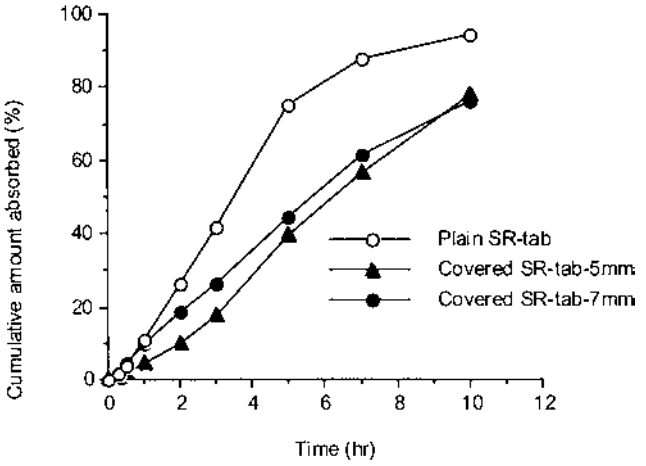


Figure 10 Absorption rates of ISDN calculated from plasma ISDN levels after administration of buccal dosage forms to dogs (Fig. 9) using a deconvolution method. (Reproduced from Ref. [4].)

Note, however, that when the hole diameter was reduced to 2 mm a very slow disintegration and absorption were observed (data not shown).

2. Drug Absorption Rates from S-DBMP-T and BCTS Systems

Iga and Ogawa calculated the drug absorption rates of isosorbide dinitrate (Fig. 10) from the S-DBMP-T and BCTS systems by a deconvolution method [4].

As previously described, the disintegration time for an S-DBMP-T system containing isosorbide dinitrate was 5 h, whereas for the BCTS system it was 10 h. The absorption rate for S-DBMP-T was calculated to be almost constant for up to 5 h and the cumulative amount absorbed after 5 h was about 80%. On the other hand, the absorption rates with BCTS systems remained almost constant for 10 h, and the cumulative amount absorbed after 10 h was about 80%. Thus, the absorption rates determined by Iga and Ogawa were consistent with the tablet disintegration rates, suggesting that the duration of absorption was determined solely by tablet disintegration time.

IV. CONCLUSION

Two types of technologies for buccal drug absorption systems have been described in this chapter based on the application of a tablet to the gingiva:

Copyright © 2003 Marcel Dekker, Inc.

S-DBMP-T for avoiding the hepatic first-pass effect of drugs and increasing their bioavailability, and BCTS for prolonging the absorption times of such drugs. To achieve high buccal bioavailability with these technologies, drugs should be incorporated that exhibit an aqueous solubility similar to, or higher than, that of propranolol (0.4 mg/mL), while the partition coefficient of the incorporated drug should be similar to, or higher than, that of lidocaine (log P = 1.5).

The feasibility of the S-DBMP-T system has been investigated using compounds such as oxendolone, propranolol, methyltestosterone, progesterone, chlormadinone acetate, and chlorpromazine. The feasibility of the BCTS technology has been investigated using the drugs glyceryl trinitrate and isosorbide dinitrate. The drug delivery technologies described in this chapter may also be useful in increasing the bioavailability of other drugs that are subject to extensive hepatic first-pass metabolism and prolonging their absorption times.

REFERENCES

1. K Iga, Y Ogawa. Buccal absorption of oxendolone in dogs after gingival administration of a slow-disintegrating tablet. J Takeda Res Lab 53:57–71, 1994.
2. K Iga, Y Ogawa. Buccal absorption of presystemically eliminated drugs in dogs after gingival administration: avoidance of first-pass elimination and increased bioavailability. J Takeda Res Lab 54:108–124, 1995.
3. K Iga, Y Ogawa. Japanese patent 61,093,113, 1986.
4. K Iga, Y Ogawa. Sustained-release buccal dosage forms for nitroglycerin and isosorbide dinitrate: increased bioavailability and extended time of absorption when administered to dogs. J Control Rel 49:105–113, 1997.
5. YV Kapila, WJ Dodds, JF Helm, WJ Hogan. Relationship between swallow rate and salivary flow. Dig Dis Sci 29:528–533, 1984.
6. W Schurmann, P Turner. A membrane model of the human oral mucosa as derived from buccal absorption performance of the β-blocking drugs atenolol and propranolol. J Pharmacol Exp Ther 30:137–147, 1978.
7. M Dellborg, G Gustafsson, K Swedberg. Buccal versus intravenous nitroglycerin in unstable angina pectoris. Eur J Clin Pharmacol 41:5–9, 1991.
8. DE Hilleman, UV Banakar. Issues in contemporary drug delivery. Part VI. Advanced cardiac drug formulations. J Pharm Tech 8:203, 1992.

Copyright © 2003 Marcel Dekker, Inc.

31

The Oral PowderJect Device for Mucosal Drug Delivery

George Costigan and Brian J. Bellhouse
University of Oxford, Oxford, England

I. INTRODUCTION

Oral PowderJect has been designed to deliver powdered drug to mucosal tissue in the mouth. Worldwide patents for the devices described below have been granted to PowderJect Pharmaceuticals plc.

There are several methods of accelerating powdered drug or vaccine particles to velocities high enough to penetrate skin or mucosal tissues. A shock tube forms the basis of the dermal PowderJect delivery device, it is capable of achieving high particle velocities in a jet of gas directed toward the target. However, the sudden release of this gas into the oral cavity was not considered desirable.

One alternative is the light gas gun in which a free piston is accelerated along a barrel by an expanding gas. Powder, placed on the upper surface of the piston, is thrown off at high velocity when the piston is brought to rest at the end of the barrel by a stopper ring. This device works well, but the possibility of piston escape or breakup at high velocity did not commend it for use in the mouth.

The Oral-PowderJect device (OPJ) uses the energy of a shock wave, travelling through a gas, to invert a flexible dome, on which the drug powder is placed. The powder is thrown off the dome with sufficient velocity to allow the particles to penetrate mucosal tissue. Gas is not released into the mouth, the dome is retained intact, and the device is relatively quiet in operation.

A clinical study on 14 adult volunteers [1] concluded that an early design of inverting dome device could safely deliver powdered lidocaine hydrochloride

Copyright © 2003 Marcel Dekker, Inc.

to the oral mucosa, without causing tissue damage. This significantly reduced the pain of a needle probe at 1 min postdelivery. In this trial there was no means of retaining the drug on the dome; therefore, it could fall off if the device was not held vertically. Consequently a number of different dome designs and manufacturing methods were investigated. Development and testing of the device to date have been focused on the delivery of lidocaine powder to the gum to produce an anesthetic effect. It is appreciated that it may be desirable to deliver other therapeutic agents by the mucosal route; the results and understanding gained from the lidocaine development program are making the achievement of this objective easier.

II. DESCRIPTION OF THE ORAL POWDERJECT

OPJ is essentially a shock tube with a closed end, which can move (the inverting dome). The theory underlying shock tube operation has been described by Glass and Patterson [2] and Anderson [3]. The performance of shock tubes with movable end walls was considered by Nabulsi et al. [4].

Figure 1 shows a cross section of an assembled prototype OPJ device. The functions of the labeled components are described below.

A. Driver Gas Reservoir

The driver gas reservoir contains high-pressure gas that is released into the rupture chamber when the plunger is depressed. The rupture chamber and shock tube normally contain air at atmospheric pressure. The driver gas in the reservoir is usually helium, since this gives the greatest shock strength when the bursting diaphragm ruptures. The pressure and volume of the driver gas are selected so that, when it is released into the rupture chamber, a pressure high enough to burst the diaphragm is achieved.

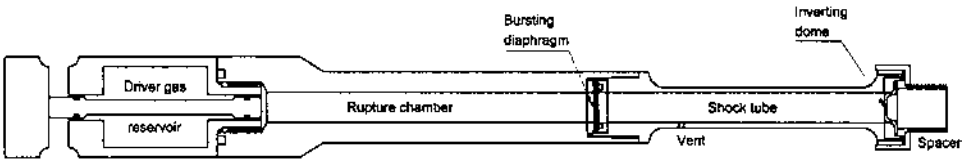


Figure 1 Components of the prototype OPJ.

Copyright © 2003 Marcel Dekker, Inc.

B. Bursting Diaphram

The diaphragm is required to burst rapidly, at a predetermined pressure, to set up the shock wave. The diaphragm burst pressure depends upon its diameter, the material used, and its thickness. Burst pressure is also influenced by the strain rate applied, with low strain rates resulting in lower burst pressures.

C. Rupture Chamber

The longer the rupture chamber is, the more time will elapse before an expansion wave, reflected from the reservoir end of the rupture chamber, catches up with—and reduces the strength of—the initial shock wave. It is desirable to ensure that this interaction occurs well after the dome has inverted.

D. Shock Tube

The shock tube diameter is fixed by the diameter of the dome. A minimum shock tube length of order five or six diameters is usually recommended, to allow a normal shock wave to form.

E. Vent

The shock tube is vented to atmosphere in the OPJ device, to allow a controlled decay of pressure and minimize the possibility of dome rupture.

F. Inverting Dome

The dome must be light and flexible to enable it to invert rapidly. It must also be resistant to rupture. It should retain drug particles under normal handling conditions, and release them uniformly when it inverts.

A prototype OPJ is shown in Figure 2.

III. DOME DESIGN

Dome design is crucial to the satisfactory performance of the OPJ and considerable effort was expended to arrive at the current design, which is still subject to refinement as our studies of dome behavior progress. The domes used to produce the results described herein were all molded from Hytrel® (Du Pont) polyester

Copyright © 2003 Marcel Dekker, Inc.

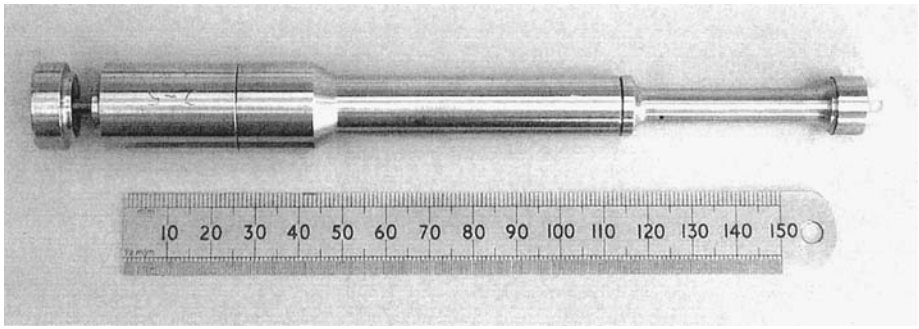


Figure 2 A prototype OPJ.

elastomer. A cross section of a typical dome is shown in Figure 3, with a photograph below it.

The domes are shaped like soup plates, with a flat base and a ridge around the outer edge, which forms a retaining seal. A total of 81 short fibers are molded into the dome base to retain the lidocaine powder. Shaking tests demonstrated that this arrangement retains 100% of a payload of 3 mg of mannitol powder (size fraction 38–53 μm) at an acceleration of 2 g and 90% at an acceleration of 6 g. Lidocaine hydrochloride powder is much less "free running" than mannitol, so the drug-loaded domes can be manipulated easily without loss of powder.

In vitro testing of these domes confirmed that their performance did not deteriorate after degreasing and sterilization with chemicals or by gamma irradiation.

IV. IN VITRO DEVICE TESTS

An instrumented version of the straight shock tube OPJ (Fig. 1) was used to collect performance data for a wide range of operating conditions. Driver cylinder pressure, rupture chamber, and shock tube pressures were recorded. The pressure measurements indicated shock strengths and velocities.

Powder velocities were deduced by cross-correlating the obscuration signals from two photo diodes. The photo diodes were illuminated by two light-emitting diodes placed 4 mm apart, with the lower beam located 10 mm above the dome clamping plane. The domes were loaded with 1.5 ± 0.5 mg of mannitol powder (size 53–75 μm) for these tests. The velocities obtained relate to the leading edge of the powder cloud as it passed through the beams. By varying

Copyright © 2003 Marcel Dekker, Inc.

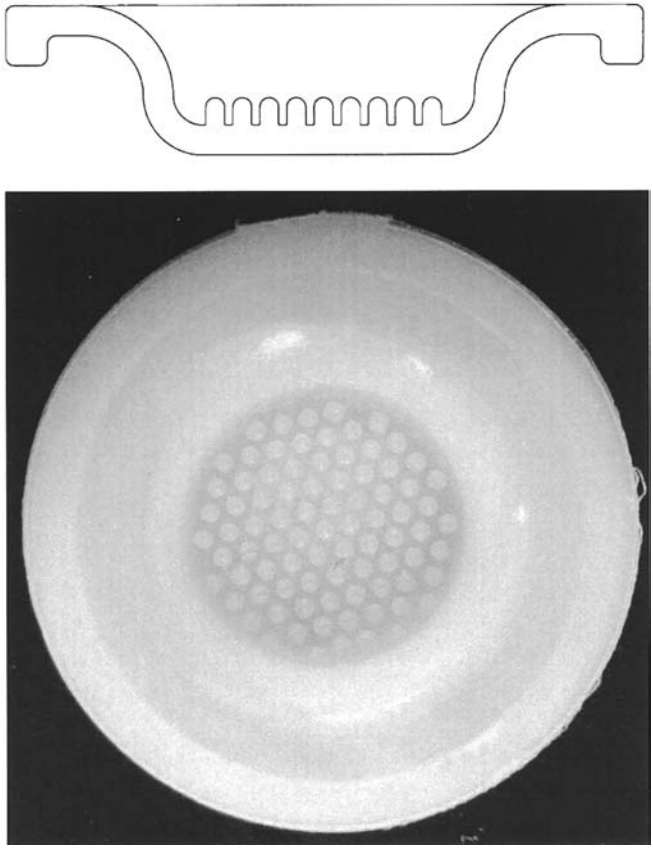


Figure 3 The injection-molded 81-fiber dome. (See color insert.)

the driver conditions, velocities between 150 and 250 m/s were achieved. The measured velocities were used as a criterion of performance of the device.

Results using particle sizes up to 800 μm (all particles with densities around 1 g/cm^3) showed that their velocities were independent of particle size for fixed driver conditions (driver gas pressure, diaphragm material and thickness, etc.). Since particle penetration depth depends upon particle size, density, and velocity, larger particles might be expected to penetrate further than small ones. This was confirmed by penetration measurements.

Oral devices were also tested by discharging them, loaded with a known payload (up to 3 mg) of model particles (usually polystyrene beads of known diameter), above a 3% agar gel target. The vented spacer fitted to the exit plane

Copyright © 2003 Marcel Dekker, Inc.

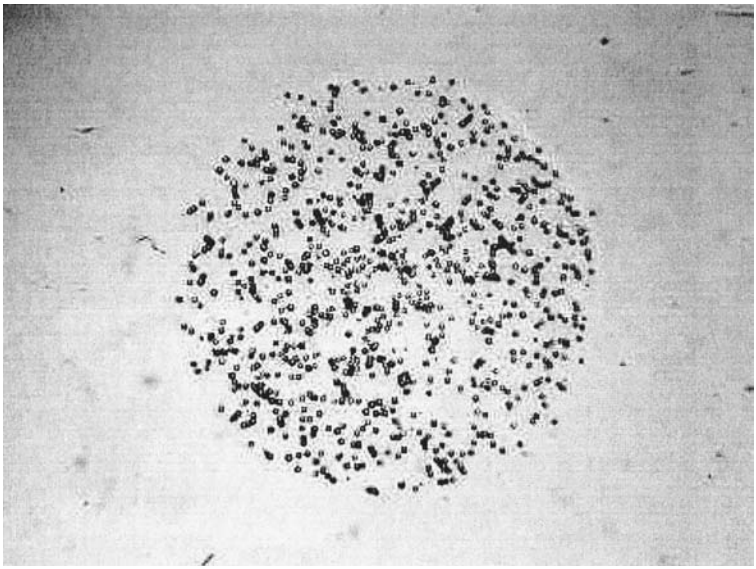


Figure 4 The OPJ footprint on agar gel target.

of each device kept it at a fixed distance from the target surface and at right angles to it. The gel surface was then photographed to record the delivery footprint. Then the gel target was sliced across a diameter and thin sections were photographed through a microscope, to establish the depth of penetration of the individual particles.

In general, the device footprint was a 6-mm-diameter circle and particles were distributed on the target in a pattern that reflected the positions of the fibers on the dome (Fig. 4).

No significant penetration was observed using 48-μm-diameter polystyrene spheres, but 99-μm-diameter particles penetrated the agar gel target to a maximum depth of 200 μm (Fig. 5).

Measurements of the penetration of similar model particles into excised mucosal tissue from pigs and dogs have also been made.

V. IN VIVO TESTS (HUMANS)

A number of small-scale, in-house clinical trials of the device were conducted in a local dental surgery. A small number of volunteers received administrations of 1.5 mg ±0.1 mg of powdered lidocaine from the OPJ device and the tolerabil-

Copyright © 2003 Marcel Dekker, Inc.

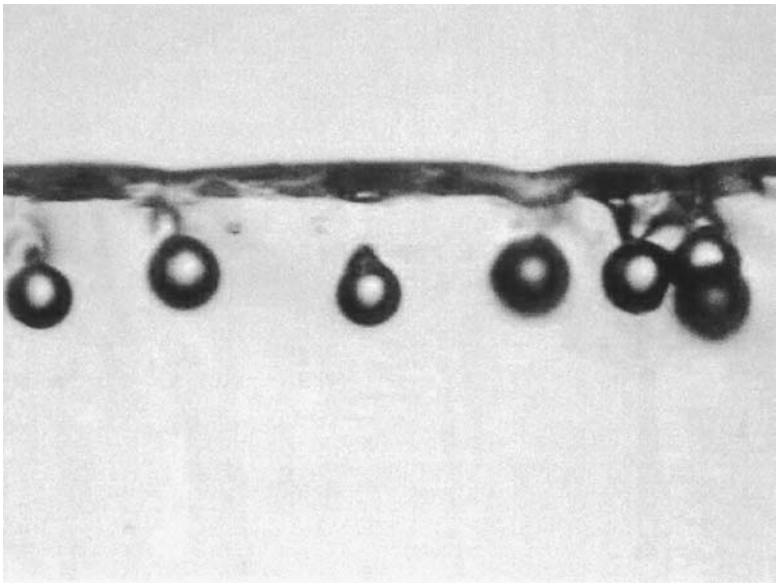


Figure 5 Penetration of 99-μm-diameter polystyrene spheres into 3% agar gel. (See color insert.)

ity and efficacy of these doses were assessed. For all tests a 5-mL 24-bar cylinder of helium was used.

A. Tolerability Tests

For tolerability testing two aluminium diaphragm thicknesses of 20 and 30 μm were used. Four particle sizes, ranging from 53 to 250 μm, were tested.

All particles were tolerated well, but the 180–250-μm-size fraction left a number of small microbleeds in the mucosal tissue.

B. Efficacy Tests

1. Experimental Methods

a. Response to a Hypodermic Needle Probe Two administrations of lidocaine (size fraction of 75–106 μm) were made to the buccal mucosa of each volunteer; a third administration of the device contained no powder. Operator and subject were unaware of which of the three administrations was the sham. Each site was probed at 30 s and 60 s after administration using a 27-g needle

Copyright © 2003 Marcel Dekker, Inc.

inserted to a depth of 1.5 mm. Pain on administration and after probing was recorded on a 100-mm VAS scale.

For the purpose of comparison 5 mg of pure lidocaine and 5 mg of sugar were placed on two sites on the buccal sulcus. Both sites were probed with a needle after 60 s. In a similar way the effect of applying a commercially available topical anesthetic gel was compared with the application of a placebo gel. Again two sites on the buccal sulcus were probed with a hypodermic needle.

b. Response to a Dental Injection Two sites on the buccal sulcus (one active, one sham) were used to test the pain of a dental injection. Lidocaine particles with diameters between 125 and 180 μm were used. After 60 s an injection of local anesthetic was administered to each site.

2. Summary of Results

The above tests have been documented by Duckworth [5], who summarized his findings as follows:

No pain on administration.
No visible tissue damage.
Anesthesia is very impressive.
Reduces the pain of a needle probe to the gum in 30 s: median VAS scores 3.3 active versus 43.2 sham.
Reduces the pain of a dental injection into the gum in 60 s: medium VAS scores 4.3 active versus 35.2 sham.
Lidocaine powder applied topically is no more effective than a placebo after 60 s.
Commercial anesthetic gel is no more effective than a placebo after 60 s.

VI. CONCLUSIONS

A typical operating condition for the existing design of OPJ uses a 5-mL cylinder of helium at 25 bar and a 30-μm aluminium bursting diaphragm to achieve powder velocities of 236 m/s. At this condition particles of 100 μm in diameter with densities around 1 g/cm^3 penetrate mucosal tissue. In-house clinical trials have demonstrated the effectiveness and speed of the OPJ in producing anesthesia in the gum.

Higher particle velocities will enable the device to deliver smaller particles into the oral mucosa. In the future a device will be designed to deliver lidocaine that is simpler and cheaper than the prototypes described here.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. GM Duckworth, HR Millward, CDO Potter, G Hewson, TL Burkoth, BJ Bellhouse. Oral PowderJect: a novel system for administering local anaesthetic to the oral mucosa. Br Dent J 185:536–539, 1998.
2. II Glass, GN Patterson. A theoretical and experimental study of shock-tube flows. J Aeronaut Sci 22:73–100, 1955.
3. JD Anderson Jr. Modern Compressible Flow. New York: McGraw-Hill, 1990.
4. SM Nabulsi, HR Millward, BJ Bellhouse. The use of a shock tube for the delivery of powdered drugs into the oral mucosa. 22nd Int. Symp. on Shock Waves, Imperial College, London, 1999, Paper #170.
5. GM Duckworth. Trial reports PJP-OPJ-BUCCAL-001 to 004, 2000.

Copyright © 2003 Marcel Dekker, Inc.

32
The PerioChip

Wilfred Aubrey Soskolne
Hebrew University–Hadassah Faculty of Dentistry, Jerusalem, Israel

I. INTRODUCTION

The PerioChip™ is a controlled-release drug delivery system that delivers the antiseptic chlorhexidine into the subgingival environment, maintaining effective levels of the drug for 6–9 days while simultaneously biodegrading. Its recommended clinical use is as an adjunct in the treatment of periodontal diseases as well as in supportive periodontal therapy. This unique delivery system is patented in Israel, the United States, 13 European countries, Australia, Canada, and Japan.

II. HISTORICAL BACKGROUND

In the 1970s it became clear that the subgingival environment was not accessible to antibacterial agents delivered to the oral cavity in the form of toothpastes and mouthwashes owing to their limited ability to penetrate into the subgingival environment [1,2]. Irrigation of the pockets with antibacterial agents was found to be clinically ineffective probably owing to the rapid washout of the drugs to ineffective levels [3,4]. This led to the development of devices that could be introduced into periodontal pockets and that would deliver their active antibacterial ingredients over an extended period of time [5–10].

At the beginning of our studies we made the strategic decision to develop a fixed-dimension delivery platform in the form of a film/slab that contained a fixed unit dose of the active agent. Based on previous studies [9,11], a prototype device to establish the proof of concept was developed. This device was an ethylcellulose film, cast from ethanol or chloroform solutions of the polymer, with a plasticizing agent and the appropriate drug incorporated into the solution [10].

Copyright © 2003 Marcel Dekker, Inc.

A number of antibacterial agents, including chlorhexidine [10,12], minocycline [13], and tetracycline [14,15], were tested in this platform and their degree of effectiveness in altering the subgingival microflora established. Based on our studies [10,12,16], chlorhexidine was chosen as the drug of choice for a number of reasons including the long history of safety and efficacy for its use in the oral cavity, its broad spectrum of antibacterial activity, no reported development of bacterial resistance, and its safety for long-term repeated multiple use.

After establishing that controlled subgingival chlorhexidine release was effective in treating periodontal disease [10,12,16] and before scaling up to a production line for clinical trials following good manufacturing practices (GMP), we made a further strategic decision to develop a biodegradable platform. Maintaining the same physical form for ease of use, a biodegradable platform would reduce the number of patient treatment visits needed and improve patient compliance compared to a nondegradable platform. A biodegradable platform, based on a cross-linked hydrolyzed gelatin matrix, was developed [17]. The final formulation was then taken through all the required regulatory steps, in the individual countries, before being marketed as the PerioChip.

III. DESCRIPTION OF PERIOCHIP

The device is in the form of a film consisting of a degradable matrix of cross-linked hydrolyzed gelatin 350 μm thick and measuring 4 mm in width and 5 mm in length. One end is rounded for ease of insertion. It weighs 7.4 mg and contains 2.5 mg of chlorhexidine digluconate (Fig. 1). It must be stored at around 4°C and has a shelf life of 2 years.

The PerioChip has a number of unique features when compared to other available technologies for the controlled subgingival delivery of drugs. These include:

It is marketed as a fixed-unit dosage for individual subgingival sites.
The placement of the device is extremely simple, taking only a few seconds.
It is the only subgingival delivery platform whose active ingredient is an antiseptic (chlorhexidine), eradicating the possible adverse effects associated with the use of antibiotics.
Its degradability.

IV. RESEARCH AND DEVELOPMENT

A. Toxicology (Perio Products Ltd.—In-House Data)

A number of studies were carried out to establish the toxicity and safety of the PerioChip in cell cultures and animal models. A study was carried out to assess

Copyright © 2003 Marcel Dekker, Inc.

Figure 1 A PerioChip is seen between a periodontal probe graduated in millimeters and a blister package containing a single chip.

the toxicity of PerioChip powder administered via gastric intubation to rats. Dosages of 7.5, 37.5, and 125 mg PerioChip powder/kg/day were administered for 30 days to groups of 24 animals. Controls received the same dosages of vehicle (PEG 400). There was no effect of the treatments on body weight, food and water consumption, hematology, or clinical chemistry parameters during the 30 days. Six animals receiving the high-dose treatment with PerioChip powder died during the study, and except for pulmonary edema noted in these six animals, gross and microscopic findings occurred with equal frequency in control and experimental animals. Therefore the "no effect" level for 30 days' oral administration of PerioChip powder was considered to be 37.5 mg/kg/day.

The effect of the chlorhexidine-containing PerioChip on the hamster cheek pouch mucosa, isolated from the oral cavity by a purse-string suture, was compared to the effect of a placebo chip, a polyvinyl chloride chip (positive control), and sham suturing without a chip. The results indicated that 7 and 14 days of exposure to the PerioChip resulted in significantly more mucosal edema than in either the sham-sutured or placebo-chip-treated groups. The polyvinyl-chloride-treated pouches resulted in significantly greater edema than did the PerioChip. The measure of erythema was similar in all three chip-treated groups and after 14 days of exposure was significantly greater than in the sham-sutured group. Histology indicated that there was slightly more inflammation in the PerioChip and polyvinyl chloride chip groups than in the placebo chip and sham-sutured groups. This difference reached significance after 14 days of exposure. All clinical and histological changes had disappeared after a 7-day recovery period. These

Copyright © 2003 Marcel Dekker, Inc.

results indicated that the PerioChip had some irritative effect on the mucosa; however, recovery was complete by 7 days.

The mice micronucleus test was carried out to establish the effect on chromosome structure in bone marrow cells following acute oral administration of different doses of PerioChip. The results indicated that, under the conditions of the test, there was no evidence of induced chromosomal or other damage leading to micronucleus formation in immature erythrocytes of treated mice 24, 48, or 72 h after oral administration of PerioChip.

A study was carried out to determine the toxicity of PerioChip powder and PerioChip matrix to Chinese hamster lung cells (V79) in the presence and absence of a rat-liver-derived metabolic activation system (S-9 mix). The PerioChip powder alone showed marked toxicity with an LC_{50} value of 17 μg/mL. The addition of S-9 mix had a detoxifying effect, giving a LC_{50} value of 57 μg/mL. PerioChip matrix was considerably less toxic with LC_{50} values of 300 μg/mL alone and 600–1000 μg/mL when S-9 mix was included. Chlorhexidine digluconate alone was extremely toxic, giving an LC_{50} of 1.5 μg/mL, which increased to 12.2 g/mL in the presence of S-9 mix.

These data indicated that, at the dosages used for the treatment of human periodontitis, the PerioChip could be considered safe for use as a therapeutic agent.

B. Pharmacokinetics

To establish the pharmacokinetics of chlorhexidine release from the PerioChip into the subgingival environment and its systemic distribution, an in vivo, open-label, single-center, 10-day pharmacokinetic study conducted on 19 volunteers with chronic adult periodontitis was carried out [18]. Each volunteer had a single PerioChip inserted into each of four selected pockets, with probing pocket depths of between 5 and 8 mm, at time 0. Gingival crevicular fluid samples were collected using filter paper strips prior to PerioChip placement and at 2 h, 4 h, 24 h, and 2, 3, 4, 5, 6, 8, and 9 days post PerioChip placement. The gingival crevicular fluid volume was measured using a calibrated Periotron™ 6000. Blood samples were collected at times 0, 1, 4, 8, and 12 h, and 5 days postdosing. Urine was collected as a total 24-h specimen, immediately postdosing and in two single samples at time 0 and 5 days. The chlorhexidine was then eluted from the paper strips and the chlorhexidine levels in gingival crevicular fluid, blood, and urine quantified using high-performance liquid chromatography. The results (Fig. 2) indicate an initial peak concentration of chlorhexidine in the gingival crevicular fluid at 2 h post PerioChip insertion (2007 μg/mL) with slightly lower concentrations of between 1300 and 1900 μg/mL being maintained over the next 96 h. The chlorhexidine concentration then progressively decreased until the conclusion of the study. Significant chlorhexidine concentrations (mean = 57 μg/mL) were

Copyright © 2003 Marcel Dekker, Inc.

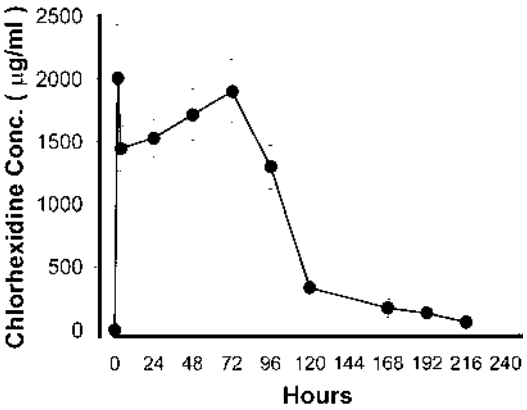


Figure 2 The mean chlorhexidine concentration in the gingival crevicular fluid from periodontal pockets treated with a single PerioChip. The vertical bars represent the standard error of the means.

still detectable at day 10. Chlorhexidine was not detectable in any of the plasma or urine samples at any time point during the study.

C. Efficacy and Safety Studies

1. As an Adjunct to Scaling and Root Planing

The efficacy and safety of the PerioChip as an adjunct to the treatment of periodontitis was established in three multicenter studies. The first was a 6-month, randomized, blinded, multicenter study of 118 patients with moderate periodontitis, carried out at three different centers in Europe [19]. A split-mouth design was used to compare the treatment outcomes of scaling and root planing alone with the combined use of scaling and root planing and the PerioChip in pockets with probing depths of 5–8 mm. The two maxillary quadrants were used for the two treatment arms of the study. Scaling and root planing was performed at baseline only, while the PerioChip was inserted both at baseline and at 3 months. Clinical and safety measurements, including probing pocket depth, probing attachment level, bleeding on probing as well as gingivitis, plaque, and staining indices, were recorded at baseline, 1, 3, and 6 months.

The average probing pocket depth reduction in the PerioChip-treated sites was significantly greater than in the sites receiving scaling and root planing alone at both 3 and 6 months with a mean difference of 0.42 mm ($p \leq 0.01$) at 6 months. The reduction in probing attachment level at the PerioChip-treated sites was greater than at the sites receiving scaling and root planing alone. The differ-

Copyright © 2003 Marcel Dekker, Inc.

ence was statistically significant at the 6-month visit only. An analysis of patients with initial probing pocket depths of 7–8 mm ($n = 47$) revealed a significantly greater reduction in probing pocket depth and probing attachment level in those pockets treated with the PerioChip compared to scaling and root planing alone at both 3 and 6 months. The mean differences between test and control sites at 6 months were, for probing pocket depth and probing attachment level, 0.71 mm and 0.56 mm, respectively.

The two other double-blind, randomized, placebo-controlled multicenter clinical trials of 9-month duration were conducted in the United States. Pooled data were reported from all 10 centers [20]. At baseline, patients free of supragingival calculus were provided with 1 h of scaling and root planing. Sites targeted for treatment were sites that bled on probing with probing pocket depths of 5–8 mm. Study sites in the PerioChip subjects received, either PerioChip plus scaling and root planing or scaling and root planing alone (to maintain study blind). Sites in placebo chip subjects received either placebo chip plus scaling and root planing or scaling and root planing alone. PerioChip placement was repeated at 3 and/or 6 months if probing pocket depths remained ≥ 5 mm. Examinations were performed at baseline, 7 days, 6 weeks, and 3, 6, and 9 months. At 9 months the PerioChip showed significantly greater reductions in both probing pocket depths (PerioChip plus scaling and root planing, 0.95 ± 0.05 mm; scaling and root planing alone, 0.65 ± 0.05 mm, $p < 0.001$: placebo chip plus scaling and root planing, 0.69 ± 0.05 mm, $p < 0.001$) and probing attachment level (PerioChip plus scaling and root planing, 0.75 ± 0.06 mm; scaling and root planing alone, 0.58 ± 0.06 mm, $p < 0.05$; placebo chip plus scaling and root planing, 0.55 ± 0.06 mm, $p < 0.05$) compared to the controls. The percentage of patients who had a probing pocket depth reduction from baseline of 2 mm or more at 9 months was 19.1% in the PerioChip group compared with 8% in the scaling and root planing controls. Adverse effects were minor and transient toothache occurred more often in the PerioChip group than in the placebo chip group ($p = 0.042$).

In a subset of 45 patients from the above U.S. multicenter study, quantitative digital subtraction radiography on standardized radiographs taken at baseline and 9 months was used to measure changes in bone height at the targeted sites [21]. Although the results showed that 15% of the sites receiving scaling and root planing alone and 11% of those receiving a placebo chip plus scaling and root planing lost bone height over the 9-month study period, none of the sites treated with the PerioChip lost bone ($p < 0.01$). Bone height gain was seen at 25% of the sites treated with the PerioChip but in only 0% and 5% of sites receiving scaling and root planing only and the placebo chip, respectively.

These data demonstrate that the adjunctive use of the PerioChip results in a significant reduction of probing pocket depths when compared with both scaling

Copyright © 2003 Marcel Dekker, Inc.

and root planing alone and the adjunctive use of a placebo chip. In addition, the PerioChip significantly reduces loss of alveolar bone.

2. In Supportive Periodontal Therapy

Having established that the subgingival controlled release of chlorhexidine is a safe and effective adjunctive chemotherapy for the treatment of periodontitis, the use of the PerioChip for the long-term management of adult periodontitis patients needed to be established. A 2-year study on 836 patients with adult periodontitis, recruited from the private offices of both periodontists and general dentists, was carried out. All patients were on supportive periodontal therapy and had completed definitive periodontal therapy at least 1 month prior to entry into the study. A PerioChip was placed in pocket sites with probing pocket depths $\geq$5 mm. Subsequently the patients continued with routine supportive periodontal therapy together with the placement of a PerioChip in pockets with probing pocket depths $\geq$5 mm every 3 months. This study has recently been completed and the data are in the process of being analyzed. An interim report of the first 72 patients to complete the study has been published [22]. The unpublished analysis of 481 patients indicates that there was a continuous decrease in probing pocket depths over and above that achieved by the definitive periodontal therapy, reaching 0.94 mm at the end of the 2-year study. The most marked decrease occurred over the first 9–12 months (Fig. 3). At 2 years, 26.2% of patients had at least two pockets showing a reduction of 2 mm or more while only 9.6% of the sites showed worsening probing pocket depths. The results indicate that the adjunctive use of the PerioChip is a clinically effective treatment option for dental professionals and their patients for long-term management of chronic periodontitis.

In a randomized, split-mouth, single-blind study [23], the effect of the placement of a single PerioChip into residual bleeding pockets with probing pocket depths $>$5 mm was examined. The patients were selected from a pool of maintenance patients at least 3 months after oral hygiene and root debridement phase therapy. At baseline all the pockets were debrided and PerioChips were placed in the pockets on one side of the mouth while those on the other side received no further treatment. The patients were examined at 1, 3, and 6 months after baseline. The results indicated a significantly greater improvement in probing pocket depths, probing attachment level, and bleeding on probing in the PerioChip-treated pockets. This benefit only became apparent at 6 months.

3. Adverse Events

Two of the clinical studies reported on adverse events occurring in patients receiving periodontal treatment including the use of the PerioChip [20,22]. The adverse events that were treatment related could be included in the categories of

Copyright © 2003 Marcel Dekker, Inc.

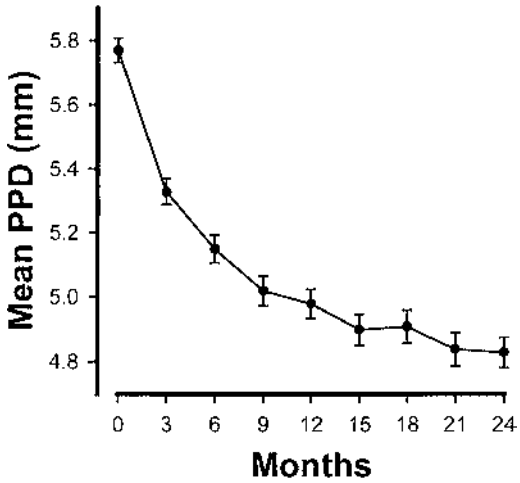


Figure 3 The mean decrease in probing pocket depths from 481 patients receiving supportive periodontal therapy and PerioChip placement in pockets ≥5 mm over the 2-year study period. The vertical bars represent the standard error of the means.

toothache or gingival swelling associated with the site of PerioChip placement. Toothache was variously described as dental, gingival, or mouth pain, or as being associated with tenderness, aching, throbbing, soreness, discomfort, or sensitivity. These symptoms occurred more frequently with the use of a PerioChip than with a placebo chip. The incidence of treatment-related adverse events is available in an interim report of a 72-patient sample of 836 patients participating in a 2-year study in which repeated applications of the PerioChip were made at 3-month intervals [22]. A total of 2568 PerioChips were placed during the study; therefore, the 83 treatment-related adverse events represents an incidence of 3.2% of PerioChip placements. However, the 83 treatment-related adverse events affected 43% of the patients over the 2-year study.

V. FUTURE DEVELOPMENTS OF THE TECHNOLOGY

The platform of the PerioChip provides the technology of delivering any drug that can be included in the PerioChip formulation to the subgingival environment. Drugs that can be used for the treatment of periodontal diseases include antibacterial, anti-inflammatory, and immunomodulatory agents and drugs that may influence bone resorption. At present we are attempting to develop a chip that can

Copyright © 2003 Marcel Dekker, Inc.

provide the controlled release of nonsteroidal anti-inflammatory drugs to the subgingival environment. Preliminary studies suggest that such a device may have a significant effect on the natural progression of periodontitis. However, many further studies need to be carried out before any relevant conclusions can be drawn.

REFERENCES

1. L Flotra. Different modes of chlorhexidine application and related local side effects. J Periodont Res 8:41–44, 1973.
2. GR Pitcher, HN Newman, JD Strahan. Access to subgingival plaque by disclosing agents using mouthrinsing and direct irrigation. J Clin Perio 7:300–308, 1980.
3. G Greenstein. Effects of subgingival irrigation on periodontal status. J Periodont 58: 827–836, 1987.
4. G Greenstein. The role of supra- and subgingival irrigation in the treatment of periodontal diseases. Position paper published by the American Academy of Periodontology. J Periodont 66: 1995.
5. JM Goodson, A Haffajee, SS Socransky. Periodontal therapy by local delivery of tetracycline. J Clin Perio 6:83–92, 1979.
6. RL Dunn, BH Perkins, JM Goodson. Controlled release of tetracycline from biodegradable fibres. J Dent Res 62:289, 1983.
7. JM Goodson, D Holborow, RL Dunn, P Hogan, S Dunham. Monolithic tetracycline-containing fibres for controlled delivery to periodontal pockets. J Periodont 54:575–579, 1983.
8. M Addy, L Rawle, R Handley, HN Newman, JF Coventry. The development and in vitro evaluation of acrylic resin strips and dialysis tubing for local drug delivery. J Periodont 53:693–699, 1982.
9. M Friedman, G Golomb. New sustained release dosage form of chlorhexidine for dental use. J Periodont Res 17:323–328, 1982.
10. A Soskolne, G Golomb, M Friedman, MN Sela. New sustained release dosage form of chlorhexidine for dental use. II. Use in periodontal therapy. J Periodont Res 18: 330–336, 1983.
11. M Donbrow, M Friedman. Timed release from polymeric films containing drugs and kinetics of drug release. J Pharm Sci 64:76–80, 1975.
12. A Stabholz, MN Sela, M Friedman, G Golomb, A Soskolne. Clinical and microbiological effects of sustained release chlorhexidine in periodontal pockets. J Clin Perio 13:783–788, 1986.
13. R Elkayam, M Friedman, A Stabholz, AW Soskolne, MN Sela, L Golub. Sustained release device containing minocycline for local treatment of periodontal disease. J Control Rel 7:231–236, 1988.
14. R Elkayam, M Friedman, A Stabholz, AW Soskolne, R Azoury. Sustained release device of tetracycline for dental use, structure and kinetics of drug release in vitro and in vivo. Proc Int Conf Pharm Tech 2:346–354, 1989.

Copyright © 2003 Marcel Dekker, Inc.

15. A Stabholz, R Elkayam, M Friedman, MN Sela, R Azoury, AW Soskolne. Clinical and microbiological evaluation of sustained release device of tetracycline in periodontal pockets. Proc Int Conf Pharm Tech 2:336–345, 1989.
16. A Stabholz, WA Soskolne, M Friedman, MN Sela. The use of sustained release delivery of chlorhexidine for the maintenance of periodontal pockets: 2-year clinical trial. J Periodont 62:429–433, 1991.
17. D Steinberg, M Friedman, A Soskolne, MN Sela. A new degradable controlled release device for treatment of periodontal disease: In vitro release study. J Periodont 61:393–398, 1990.
18. WA Soskolne, T Chajek, M Flashner, et al. An in vivo study of the chlorhexidine release profile of the PerioChip in the gingival crevicular fluid, plasma and urine. J Clin Perio 25:1017–1021, 1998.
19. WA Soskolne, PA Heasman, A Stabholz, et al. Sustained local delivery of chlorhexidine in the treatment of periodontitis: a multi-center study. J Periodont 68:32–38, 1997.
20. MK Jeffcoat, KS Bray, SG Ciancio, et al. Adjunctive use of a subgingival controlled-release chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planing alone. J Periodont 69:989–997, 1998.
21. MK Jeffcoat, KG Placanis, TW Weatherford, M Reese, NC Geurs, M Flashner. Use of a boidegradable chlorhexidine chip in the treatment of adult periodontitis: clinical and radiological findings. J Periodont 71:256–262, 2000.
22. A Stabholz, L Shapira, D Mahler, et al. Using the PerioChip in treating adult periodontitis: an iterim report. Compend Contin Edu Dent 21:325–338, 2000.
23. PA Heasman, L Heasman, F Stacey, GI McCraken. Local delivery of chlorhexidine gluconate (PerioChip) in periodontal maintenance patients. J Clin Perio. 28:90–95, 2001.

Copyright © 2003 Marcel Dekker, Inc.

33

Polysaccharide-Based Mucoadhesive Buccal Tablets

Hemant H. Alur,* Ashim K. Mitra, and Thomas P. Johnston
University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.

I. INTRODUCTION

The oral cavity is an attractive site for drug delivery. It offers the advantages of ease of administration, patient acceptability, ease of removal, and termination of dosage at will, among others. In addition, it lends itself to a range of simple delivery systems ranging from solution and tablets to the more complex patch formulations. This chapter describes the background theory and rationale for developing polysaccharide-based mucoadhesive buccal tablets for protein delivery and describes the research that has been conducted on this technology.

II. DESIGN CONSIDERATIONS

A. Reasons for Selecting the Oral Mucosal Route

In recent years, proteins and peptides have emerged as a major class of therapeutic agents. To successfully deliver such compounds in clinically efficacious amounts, pharmaceutical scientists are faced with the challenges of (a) selection of a suitable route of drug delivery, and (b) appropriate formulation of these bioengineered drugs to enhance absorption and prevent degradation at the site of administration. The most common route of protein and peptide drug delivery has been the parenteral route. However, this route is associated with pain on administration resulting in poor patient compliance, and the formulation needs to be sterile. In

* *Current affiliation*: Murty Pharmaceuticals, Inc., Lexington, Kentucky, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Chronological Survey of In Vivo Experiments on Buccal Delivery of Peptides and Proteins

Author(s) (Reference)	Year	Peptide (in vivo model)
Dillon et al. [23]	1960	Pitocin (human)
Miller [24]	1973	Oxytocin (human)
Dawood et al. [25]	1980	Oxytocin (human)
Ishida et al. [26]	1981	Insulin (dog)
Anders et al. [27]	1983	Protirelin (human)
Schurr et al. [28]	1985	Protirelin (human)
Aungst and Rogers [29]	1988	Insulin (rat)
Aungst et al. [30]	1988	Insulin (rat)
Nakada et al. [31]	1988	Calcitonin (rat)
Ritschel et al. [32]	1989	Insulin (dog)
Ho and Barsuhn [33]	1989	Protirelin, oxytocin (dog)
Oh and Ritschel [34]	1990	Insulin (rabbit)
Wolany et al. [35]	1990	Octreotide (dog)
al-Achi and Greenwood [36]	1993	Insulin (rat)
Heiber et al. [37]	1994	Calcitonin (dog)
Bayley et al. [38]	1995	Recombinant human interferon-α B/D hybrid (rat, rabbit)
Gutniak et al. [39]	1996	Glucagon-like peptide I (human)
Nakane et al. [40]	1996	Leuteinizing-hormone-releasing hormone (dog)
Hoogstraate et al. [41]	1996	Buserelin (pig)
Li et al. [42]	1997	Thyrotropin-releasing hormone (rat)
Li et al. [43]	1997	Oxytocin (rabbit)
Alur et al. [44]	1999	Calcitonin (rabbit)

contrast, drugs administered by the gastrointestinal route are subjected to acid hydrolysis and extensive gut and/or hepatic "first-pass" metabolism. Thus, protein and peptide drugs may exhibit poor oral bioavailability via this route. Several noninvasive transdermal and mucosal routes are available that offer effective and viable alternatives for systemic drug delivery. However, the transdermal delivery route is limited to potent, lipophilic compounds, does not provide rapid blood levels, and is less permeable than other mucosae [1,2]. Mucosal routes have been investigated extensively for systemic drug delivery. These investigations have identified certain drawbacks that limit extensive utilization of the nasal, ocular, pulmonary, rectal, and vaginal routes [3–5]. However, the buccal and sublingual routes do not exhibit many of these limitations, and many investigators have attempted to deliver drugs across the oral mucosa, including proteins and peptides (Tables 1 and 2).

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Data from In Vivo Experiments on Buccal Delivery of Peptides and Proteins

Peptide/ protein	MW (Da)	Species				
		Rat	Rabbit	Dog	Pig	Human
TRH	362	—	—	—	—	4%
Oxytocin	1,007	—	0.1%	—	—	<10%
LHRH	1,182	—	—	0.41% (alone) 0.34–1.62% (with enhancers)	—	—
Buserelin (analog of LHRH)	~1,182	—	—	—	1% (alone) 5% (with enhancers)	—
Calcitonin	3,432	—	16 and 37%	550 IU over 6 h	—	—
GLP-I	4,169	—	—	—	—	7% (7–36-amide fragment)
Insulin	5,808	0% (alone) 25% (with enhancers)	0% (alone) 5% (with enhancers)	0% (alone) 0.5% (with enhancers)	—	0–4%
IFN α-B/D hybrid	19,000	<1%	<1%	—	—	

Copyright © 2003 Marcel Dekker, Inc.

The major mechanism of drug transport across buccal mucosa appears to be by passive (simple Fickian) diffusion [6]. Endocytotic processes are not apparent in buccal epithelium [6]; however, there is considerable evidence for the presence of carrier-mediated transport in the buccal mucosa for nutrients such as glucose [7], amino acids [8,9], glutathione [10], thiamine [11], nicotinic acid [12], monocarboxylic acids [13,14], and the aminocephalosporin antibiotic cefadroxil [15]. The premise of passive transport as the mechanism of peptide and protein absorption across the buccal mucosa is widely accepted [16,17]. In addition, it can be seen from the data presented in Table 2 that, in general, as the molecular weight of the peptide increases, the bioavailability decreases. This suggests that the peptides and proteins, being hydrophilic and globular in nature, are transported by the paracellular route.

The data discussed in this section highlighted to us the potential of the oral mucosa as a portal for protein administration to the systemic circulation. Therefore, we considered the oral mucosa attractive for the development of a mucoadhesive tablet for protein delivery.

B. Enzymatic Degradation

Despite these advantages, the oral mucosal route does exhibit some disadvantages, which may limit its use for the delivery of proteins and peptides. The bioavailability of therapeutic polypeptides and proteins via this route is generally very low ($<5\%$) owing to their low lipid solubility and inherent large molecular weight. In addition, although a major advantage of the buccal route is that it avoids the acid- and enzyme-mediated degradation and hepatic first-pass metabolism associated with the gastrointestinal tract [2,18], degradation of proteins and peptides by enzymes such as aminopeptidases, carboxypeptidases, several endopeptidases, and esterases can occur in the buccal mucosa and contributes to their low bioavailability.

Indeed, the proteolytic activity of the buccal mucosa presents a significant challenge to the development of a buccal tablet designed to deliver proteins and peptides. Many buccal homogenate studies have provided initial data concerning the rate and extent of biochemical degradation of peptides when delivered by the buccal route. However, the inability of these investigations to distinguish between cytosolic, membrane-bound, and intercellular proteolytic activity remains a limitation of these investigations. This is because protein and peptide transport can be either trans- or paracellular in nature; therefore, when formulating a buccal tablet it is important to know the exact location of these proteolytic enzymes. For these reasons we conducted enzyme studies to assist in the rational design and development of the polysaccharide-based mucoadhesive buccal tablet.

Copyright © 2003 Marcel Dekker, Inc.

C. Use of Mucoadhesive Polymers

Two specific properties of the delivery system, immobilization on the oral mucosa and a capacity for controlled release, were considered important characteristics to build into the buccal formulation.

With any buccal drug delivery system there is a high likelihood of a major fraction of drug being lost (a) due to accidental swallowing of the dosage form, or (b) by salivary washout of the tablet. These processes limit drug absorption from the oral cavity. Therefore, retention of the dosage form in the oral cavity was considered an important aspect of the polysaccharide-based mucoadhesive buccal delivery system. We believed that retention could be optimally achieved by the inclusion of polysaccharide-based mucoadhesive polymers in the formulation. An additional advantage this would impart on the delivery system would be that it would promote intimate contact between the drug formulation and the oral mucosa thereby maintaining a high drug concentration at the absorptive surface and protecting the drug from environmental degradation.

It has been shown that polymers such as derivatives of poly (acrylic acid), polycarbophil, and carbomer can protect therapeutically important proteins and peptides from proteolytic activity of enzymes, endopeptidases (trypsin and α-chymotrypsin), exopeptidases (carboxypeptidases A and B), and microsomal and cytosolic leucine aminopeptidase. However, cysteine protease (pyroglutamyl aminopeptidase) may not be inhibited by polycarbophil and carbomer [19], which therefore limits the use of these commonly used pharmaceutical excipients in buccal formulations. This limitation led us to investigate other protective bioadhesive polymers for buccal applications and research polysaccharide-based mucoadhesives for use as tablet excipients in buccal dosage forms. A final advantage, therefore, of our selection of polysaccharide-based mucoadhesive polymers is that they may protect incorporated proteins and peptides from proteolytic activity of enzymes.

D. Formulation Considerations

Tablet formulations were selected as the dosage form of choice because of their range of formulation capabilities, ease of manufacture, and availability of tabletting manufacturing equipment. Bioadhesive tablets may be either monolithic or multilayered devices (Fig. 1). Monolithic tablets offer the advantages that they can be prepared by conventional techniques (either direct compression or wet granulation), and they provide the possibility of holding large amounts of drug. Using either compression or spray coating, it is theoretically possible, using a water-impermeable material such as cellophane, hydrogenated castor oil, teflon, ethyl cellulose, etc., to impart a coating on every face of the formed tablet except

Copyright © 2003 Marcel Dekker, Inc.

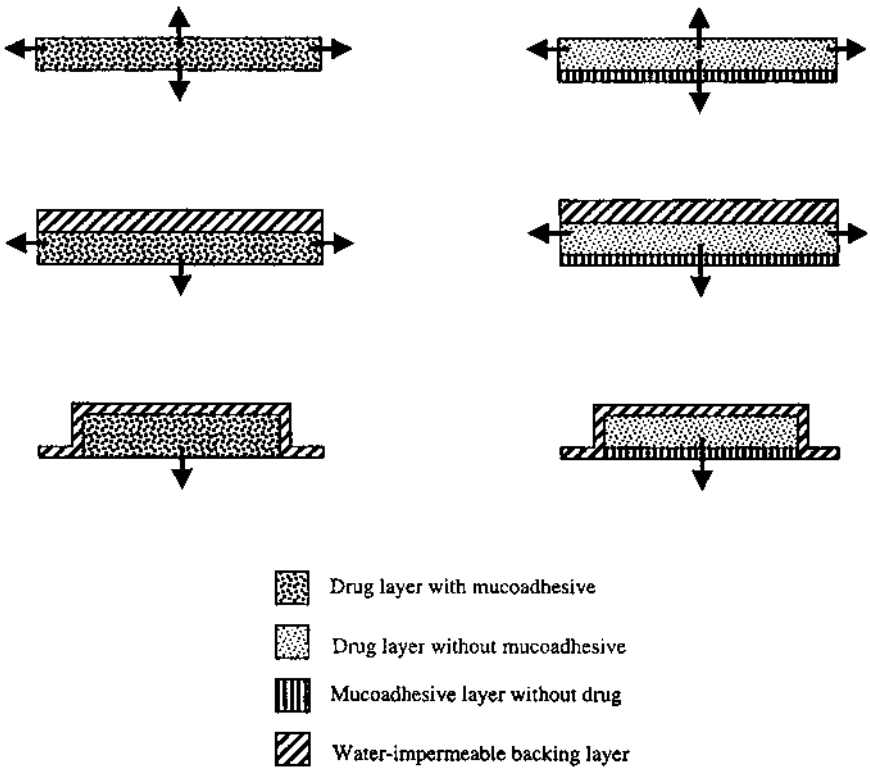


Figure 1 Schematic diagram showing the geometric designs of buccal delivery devices. (From Ref. [19].)

the one that will be in contact with the mucosa. This provides the opportunity to impart a unidirectional drug release to the tablet. Multilayered tablets can easily be prepared by adding each formulation ingredient layer by layer into a die and compressing it on a tablet press. Another advantage of tablet dosage form for buccal administration is that tablets can be designed to deliver drugs either systemically via, or locally to, the oral cavity. A final advantage is that the incorporation of mucoadhesive components into the formulation is a relatively easy process and would aid in optimizing bioadhesion. Although several mucoadhesive polymers have been shown to be useful for buccal drug delivery (Table 3), given the excellent mucoadhesive properties of polysaccharide-based polymers, we considered it would be worthwhile investigating and evaluating polysaccharide-based polymers in buccal drug delivery systems.

Copyright © 2003 Marcel Dekker, Inc.

Table 3 Muco/bioadhesive Polymers

Synthetic polymer	Natural polymer
Hydroxypropylcellulose (HPC)	Acacia
Polyacrylic acid	Tragacanth
Polymethylmethacrylate (PMMA)	Gelatin
Sodium carboxymethylcellulose (NaCMC)	Chitosan
Methylcellulose (MC)	λ-Caragenan
Polyvinyl pyrrolidone (PVP)	Xanthan gum
Polyvinyl alcohol (PVA)	Sodium alginate
Hydroxyethylcellulose (HEC)	Guar gum

III. RESEARCH AND DEVELOPMENT

A. Objectives

The objectives of this research were (a) to develop and evaluate a unidirectional, sustained-release, mucoadhesive buccal tablet using the natural gum, *Hakea*, and (b) to delineate the mechanisms underlying the sustained-release, mucoadhesive, and enzyme inhibition properties of the gum. Calcitonin (CT), a 32-amino-acid polypeptide, functioning as a hypocalcemic agent, is used in the treatment of Paget's disease, hypercalcemia, and osteoporosis. Treatment calls for daily or alternate-day subcutaneous (SC) or intramuscular (IM) injections for an extended period. This is bothersome and inconvenient for patients. Thus, the mucosal route offers an effective alternative for systemic drug delivery. The buccal mucosa avoids the harsh environment of the gastrointestinal tract and first-pass metabolism. Salmon calcitonin (sCT) represents one of the calcitonins and is currently available only in a sterile solution for SC and IM injection and nasal spray form.

Hakea is a water-soluble polysaccharide exudate from the plant *Hakea gibbosa* (Fam: Proteaceae) indigenous to New South Wales, Australia. The gum [20] consists of various sugars, including arabinose, xylose, mannose, galactose, and glucuronic acid in a 6:1.5:1:8:2.5 ratio, and has an average molecular weight of greater than 2×10^6 Da. The gum is completely water soluble at a concentration of 2% (w/v) at room temperature. The structure of the gum is shown in Figure 2. The gum consists of a core and four branches (R^1, R^2, R^3, and R^4). The core consists of alternating units of glucopyranosyl and mannopyranosyl units [20,21]. The gum was purified by filtration of a 2% (w/v) solution through a muslin cloth and then freeze-dried.

Formulation of buccal tablets involved preparation of two types of tablets: type I, a matrix-type core tablet prepared by direct compression, and type II, a tablet in which all but one face of the core tablet was coated with Cutina® by compression coating so as to render unidirectional release of the incorporated

Copyright © 2003 Marcel Dekker, Inc.

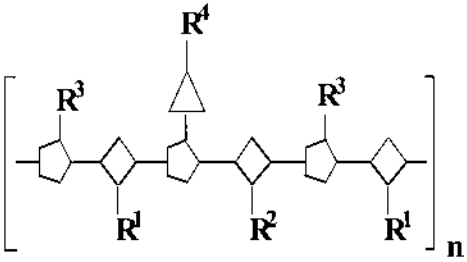


Figure 2 Chemical structure of the natural gum from *Hakea gibbosa*. (From Refs. [20,21].)

peptide. Cutina®, or hydrogenated castor oil, was used to coat the core tablets since it is insoluble in water. The rationale for developing unidirectional-release, mucoadhesive buccal tablets was that salivary washout of sCT would be minimized.

B. In Vitro Studies

1. Dissolution/Release Study

In vitro release profiles (Fig. 3) from buccal tablets containing 0, 12, and 32 mg *Hakea* with 40 μg of sCT were sigmoidal in nature and consisted of an initial slow-releasing phase followed by a linear phase, where the release appeared to follow zero-order kinetics. The mechanism of in vitro release was determined from the values of n obtained by modeling the first 60% of the peptide released to Eq. (1):

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where, M_t/M_∞ = fraction of drug released, k = kinetic constant, t = time, and n = diffusional exponent. The mechanism of drug release may be Fickian diffusion when the value of $n = 0.5$, anomalous (non-Fickian) transport when $0.5 < n < 1.0$, and case II transport when $n = 1.0$. A value of n greater than 1 signifies super case II transport as the mechanism of drug release [22]. In our experiments the values for the diffusional exponent (n) were greater than 1, indicating that the mechanism of sCT release was super–case II transport. That is, the release of sCT from the buccal tablets was likely due to the combination of polypeptide diffusion and polymer relaxation/dissolution as opposed to simple Fickian diffusion. This mechanism also explains the initial slow-release phase where the polymer was not completely hydrated, resulting in an incomplete relax-

Copyright © 2003 Marcel Dekker, Inc.

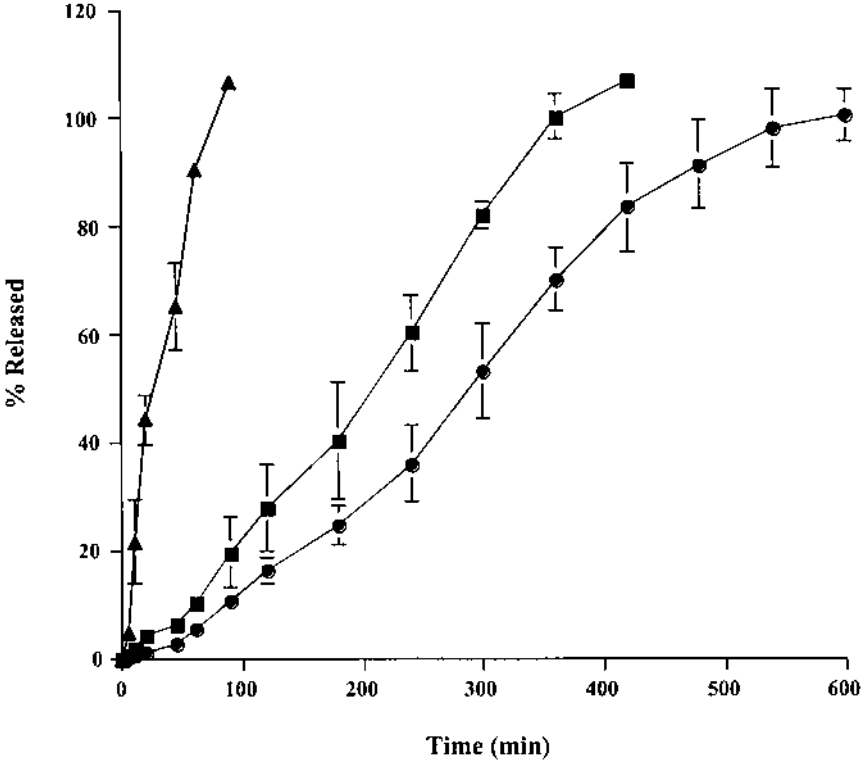


Figure 3 In vitro release profiles of sCT from directly compressed tablets that contained 40 μg sCT and 0 mg *Hakea* (▲), 12 mg *Hakea* (■), or 32 mg *Hakea* (●).

ation of the side chains. Insufficient hydration would lead to the creation of a channel/pore network through which the free diffusion of sCT would be hindered. Upon complete hydration, the *Hakea* began to dissolve with subsequent relaxation of the side chains.

2. Muco/Bioadhesion Study

It can be seen from Figure 4 that the mean values of the force of detachment increased with time and reached a plateau at later time points, suggesting that the process of bioadhesion is saturable and that the mechanism of bioadhesion is likely due to chain interpenetration and physical entanglement of *Hakea* with the mucus. The fact that the bioadhesive strength reaches a plateau at later time points could be due to the limited surface area of the uncoated tablet face and

Copyright © 2003 Marcel Dekker, Inc.

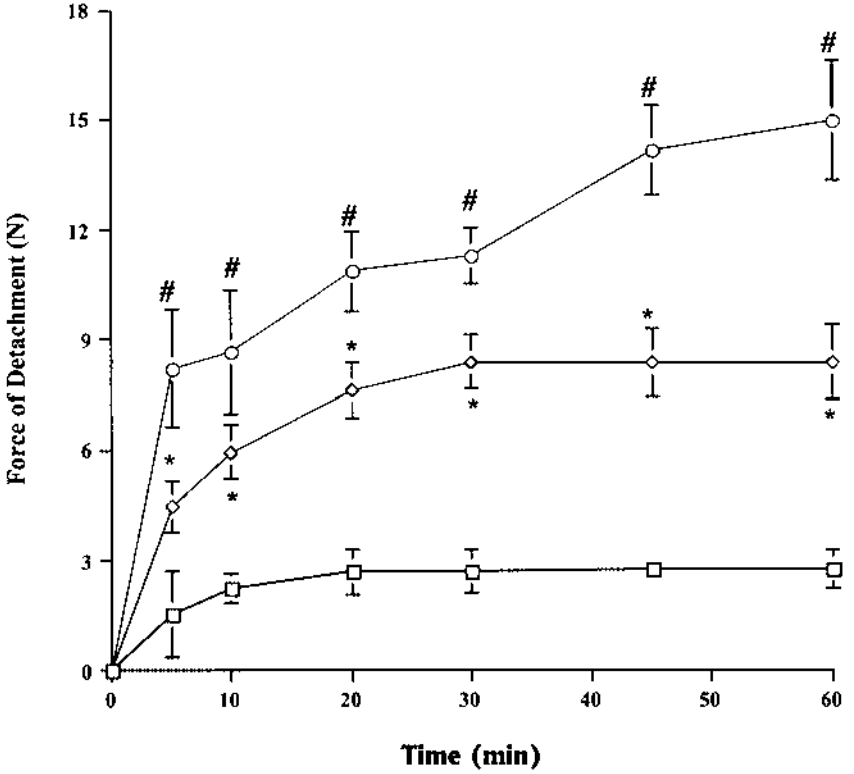


Figure 4 The force of detachment from excised rabbit intestinal mucosa for directly compressed buccal tablets that contained 40 μg sCT and 0 mg *Hakea* (□), 12 mg *Hakea* (◇), or 32 mg *Hakea* (○). #,* Indicates a statistically significant value.

exhaustion of a finite number of points of the gum, which can entangle with mucus in the circular surface area covered by the mucoadhesive tablet. A potential reason for an increase in the mucoadhesive bond strength with increasing *Hakea* content may be due to enhanced water uptake by the gum resulting in gum swelling and mobilization of flexible polysaccharide chains for interpenetration and physical entanglement with the mucus.

3. Enzyme Kinetics Study

The enzyme kinetic studies were conducted at 37°C in 100 mM potassium phosphate buffer (pH 8.0) with 10 mM EDTA, 5% (v/v) glycerol, and 5 mM DTT

Copyright © 2003 Marcel Dekker, Inc.

for 15 min with 0, 0.1, 0.25, 0.75, 1.25, and 2% (w/v) of the gum. Enzymatic activity was determined by a colorimetric assay using the specific substrate L-pyroglutamic acid β-naphthylamide. Stock solutions (1.25, 2.5, 5, 10, and 20 mM) of L-pyroglutamic acid β-naphthylamide (substrate) were prepared in absolute methanol. The velocity of the reaction catalyzed by pyroglutamate aminopeptidase was determined by the amount of the product (β-naphthylamine) liberated at each substrate and gum concentration. It is evident from Figure 5 that as the percent of *Hakea* was gradually raised in the buffer, the velocity of the reaction decreased. As the concentration of the gum was gradually increased, the mean values for V_{max} decreased, while the mean values for K_s increased (Table 4). The mean values for k_{cat} also decreased with a gradual increase in the concentration of the gum (Table 4).

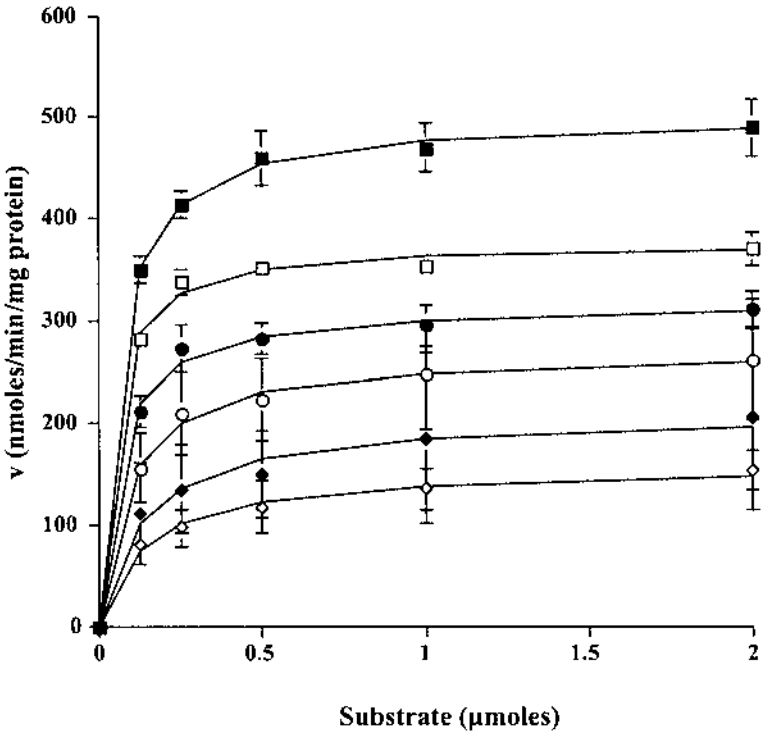


Figure 5 Typical enzyme kinetic plot of initial velocity against L-pyroglutamic acid β-naphthylamide concentration in the absence (■) and presence of 0.1% (□), 0.25% (●), 0.75% (○), 1.25% (◆), and 2% (◇) of *Hakea*.

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Kinetic Parameters of Pyroglutamate Aminopeptidase

Hakea (%)	V_{max} (nmoles/min/mg protein)	K_s (μM)	k_{cat} (min^{-1})	Time for one catalytic cycle (s)
0	502.95 ± 28.90	24.40 ± 2.14	14.09 ± 0.81	4.27 ± 0.24
0.1	377.83 ± 4.57	17.42 ± 4.60	10.58 ± 0.13	5.67 ± 0.07
0.25	318.94 ± 21.46*	25.76 ± 4.22	8.93 ± 0.60	6.74 ± 0.44
0.75	272.17 ± 63.41*	39.70 ± 21.63	7.62 ± 1.78	8.18 ± 2.03
1.25	211.32 ± 91.27*	58.48 ± 12.41†	5.92 ± 2.56	11.30 ± 4.09‡
2	158.83 ± 24.5*	63.03 ± 1.89†	4.45 ± 0.69	13.69 ± 1.98‡

*,†,‡ Indicates a statistically significant value.

C. In Vivo Studies

The plasma sCT concentration-versus-time profiles (Figs. 6 and 7) following administration of the 40 μg sCT buccal tablet with either 12 or 32 mg of *Hakea* to New Zealand white rabbits clearly indicates that *Hakea* effectively sustained the release of sCT from the buccal tablets in vivo as well. The relevant pharmacokinetic parameters are listed in Table 5. The plasma sCT levels obtained in this investigation using sCT buccal tablets that contained *Hakea* were greater than therapeutic plasma levels (0.1–0.4 ng/mL). These levels were achieved without the use of a permeation enhancer. The C_{max} and C_{min} decreased while the t_{max} increased with an increase in the amount of *Hakea* contained in the tablet (Figs. 6 and 7). The pharmacodynamic response demonstrated that the dual compaction process during the manufacturing of the tablet did not adversely affect sCT's biological activity.

IV. CONCLUSION

In conclusion, the ability of the novel gum *Hakea gibbosa* to sustain the release of sCT has been demonstrated both in vitro and in vivo. In addition, the gum was demonstrated as being functionally effective as a mucoadhesive excipient and enzyme inhibitor of the model enzyme pyroglutamate aminopeptidase. The mucoadhesive tablets were convenient to apply and remove from the buccal mucosa and did not appear to damage the underlying tissue.

Recent years have witnessed an explosive growth in our understanding of the mechanisms associated with the absorption of drugs, especially therapeutic peptides and proteins. Scientists from a variety of disciplines continue to elucidate the variables associated with the optimal formulation and delivery of drugs via

Copyright © 2003 Marcel Dekker, Inc.

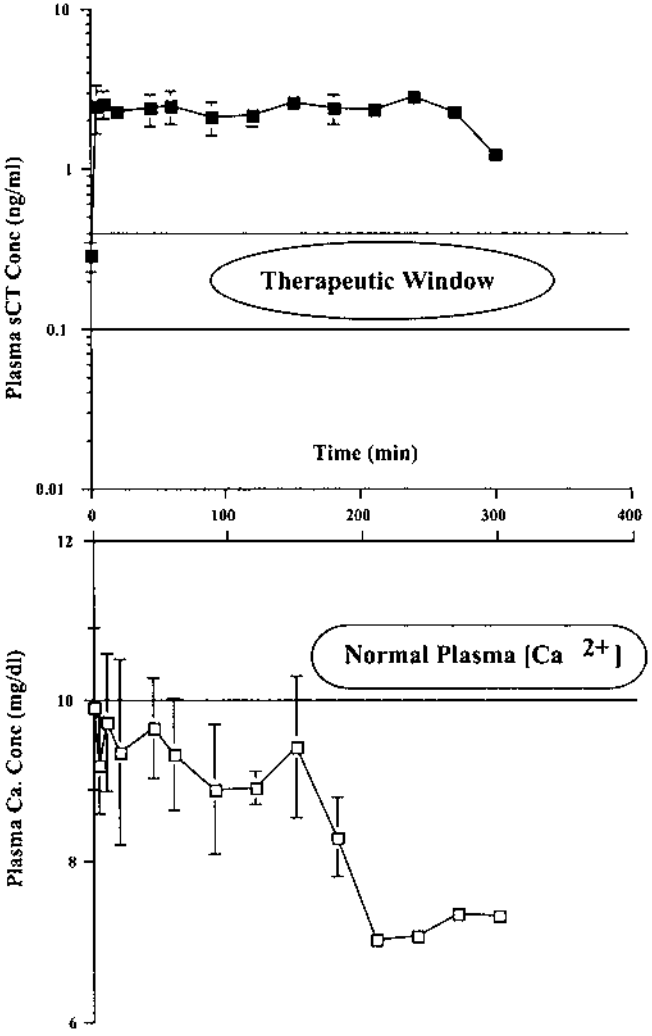


Figure 6 Plasma profiles of sCT (■) and calcium (□) in rabbits following the application of buccal tablets containing 40 μg (200 IU) of sCT and 12 mg of *Hakea*. Buccal tablets were removed at 180 min.

Copyright © 2003 Marcel Dekker, Inc.

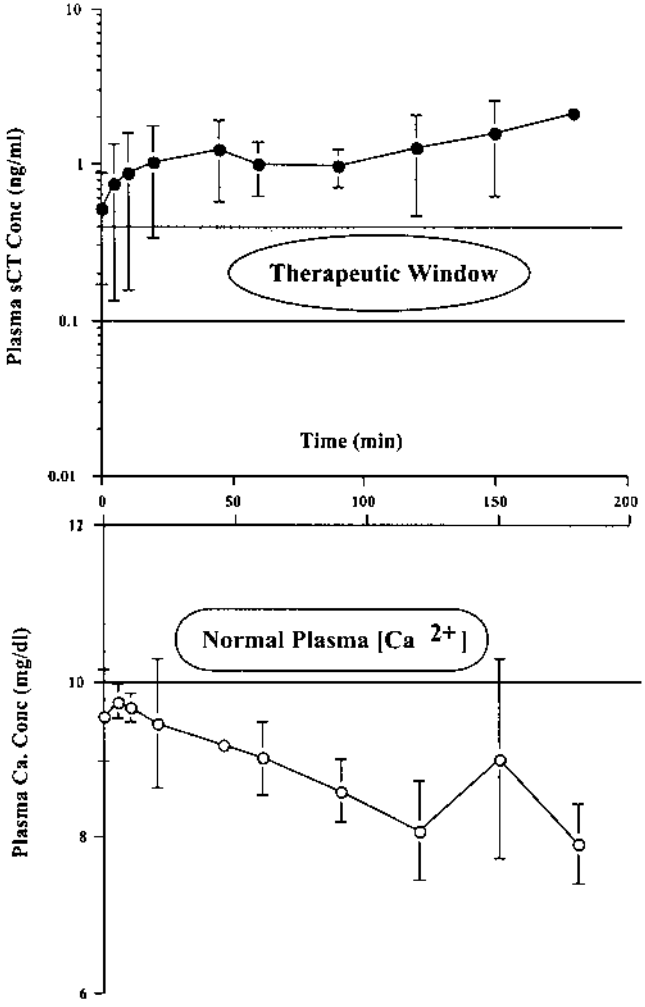


Figure 7 Plasma profiles of sCT (●) and calcium (○) in rabbits following the application of buccal tablets containing 40 μg (200 IU) of sCT and 32 mg of *Hakea*.

the oral mucosa. A greater understanding of the para- and transcellular route of drug absorption, proteolytic enzyme activity that may potentially degrade therapeutic peptides, and simultaneous degradation of compounds during the mucosal transport process is essential to the development of buccal delivery systems. Moreover, methods to increase drug flux (e.g., use of permeation enhancers) with-

Copyright © 2003 Marcel Dekker, Inc.

Table 5 Pharmacokinetic Parameters of sCT Following Application of Mucoadhesive Tablets to the Buccal Mucosa of New Zealand Albino Rabbits

Pharmacokinetic parameter	40 μg sCT and 12 mg *Hakea*	40 μg sCT and 32 mg *Hakea*
$AUC_{0-2\ hr}\left(\frac{ng \times min}{mL}\right)$	273 ± 49*	125 ± 63
CL (ml/min/kg)	19 ± 3.3	18 ± 0.4
F (%)	37 ± 6†	16 ± 8
C_{max} (ng/mL)	2.50 ± 0.5	1.33 ± 0.65
C_{min} (ng/mL)	2.00 ± 0.2	0.68 ± 0.41
t_{max} (min)	70 ± 17	140 ± 17
$AAC_{0-2\ hr}$ (mg·min/dL)[a]	74 ± 35	71 ± 59

[a] Area above the calcium reduction curve.
*,† Indicates a statistically significant value.

out associated toxicity, strategies to inactivate proteolytic enzymes, and innovative approaches with regard to controlled drug delivery and mucoadhesive dosage forms will all improve the delivery of drug substances via the oral cavity.

ACKNOWLEDGMENTS

This work was supported in part by University of Missouri research board grant (TPJ) and NIH grants (AI 36624, EY 09171 and EY 10659; AKM).

REFERENCES

1. CA Lesch, CA Squier, A Crutchley, DM Williams, P Speight. The permeability of human oral mucosa and skin to water. J Dent Res 68:1345–1349, 1989.
2. MJ Rathbone, BK Drummond, IG Tucker. The oral cavity as site for systemic drug delivery. Adv Drug Del Rev 13:1–22, 1994.
3. Z Marom, J Shelhamer, M Kaliner. Nasal mucus secretion. Ear Nose Throat J 63: 36, 1984.
4. HJM van de Donk, AGM Van der Heuvel, J Zuidema, FWHM Merkus. The effects of nasal drops and their additives on human nasal mucociliary clearance. Rhinology 20:127, 1982.
5. AG de Boer, DD Breimer, H Mattie, J Pronk, JM Gubbens-Stibbe. Rectal bioavailability of lidocaine in man: partial avoidance of "first-pass" metabolism. Clin Pharmacol Ther 26:701–709, 1979.
6. IA Siegel, SH Hall, R Stambaugh. Permeability of the oral mucosa. In: CA Squier,

Copyright © 2003 Marcel Dekker, Inc.

J Meyer, eds. Current Concepts of the Histology of Oral Mucosa. Springfield, IL: Charles C Thomas, 1971, p. 274.
7. AS Manning, DF Evered. The absorption of sugars from the human buccal cavity. Clin Sci Mol Med 51:127–132, 1976.
8. DF Evered, JV Vadgama. Absorption of amino acids from the human buccal cavity. Biochem Soc Trans 9:132–133, 1981.
9. RB Gandhi. Some permselectivity and permeability characteristics of rabbit buccal mucosa. Ph.D. thesis, University of Wisconsin, Madison, 1990.
10. MK Hunjen, DF Evered. Absorption of glutathione from the gastro-intestinal tract. Biochem Biophys Acta 815:184–188, 1985.
11. DF Evered, C Mallet. Thiamine absorption across human buccal mucosa in vivo. Life Sci 32:1355–1358, 1983.
12. DF Evered, F Sadoogh-Abasian, PD Patel. Absorption of nicotinic acid and nicotinamide across human buccal mucosa in vivo. Life Sci 27:1649–1661, 1980.
13. N Utoguchi, Y Watanabe, T Suzuki, J Maehara, Y Matsumoto, M Matsumoto. Carrier-mediated transport of monocarboxylic acids in primary cultured epithelial cells from rabbit oral mucosa. Pharm Res 14:320–324, 1997.
14. N Utoguchi, Y Watanabe, Y Takase, T Suzuki, M Matsumoto. Carrier-mediated absorption of salicylic acid from hamster cheek pouch mucosa. J Pharm Sci 88:142–146, 1999.
15. Y Kurosaki, H Nishimura, K Terao, T Nakayama, T Kimura. Existence of specialized absorption mechanism for cefadroxil, an aminocephalosporin antibiotic, in human oral cavity. Int J Pharm 82:165–169, 1992.
16. RB Gandhi, JR Robinson. Oral cavity as a site for bioadhesive drug delivery. Adv Drug Del Rev 13:43–74, 1994.
17. HE Junginger, JA Hoogstraate, JC Verhoef. Recent advances in buccal drug delivery and absorption—in vitro and in vivo studies. J Control Rel 62:149–159, 1999.
18. HH Alur, TP Johnston, AK Mitra. Peptides and proteins: buccal absorption. In: J Swarbrick, JC Boylan, eds. Encyclopedia of Pharmaceutical Technology. Vol. 20. New York: Marcel Dekker, 2001, pp. 193–218.
19. HL Luessen, JC Verhoef, G de Boer, HE Junginger, BJ de Leeuw, G Borchard, CM Lehr. Multifunctional polymers for the peroral delivery of peptide drugs. In: E Mathiowitz, DE Chickering III, CM Lehr, eds. Bioadhesive Drug Delivery Systems. New York: Marcel Dekker, 1999, p. 299.
20. PFK Eagles. Structures of complex plant polysaccharides, exudates from *Hakea sericea* and *Hakea gibbosa*. Ph.D. thesis, Department of Chemistry, University of Capetown, South Africa, 1992.
21. HH Alur, SI Pather, TP Johnston, AK Mitra. Evaluation of the gum from *Hakea gibbosa* as a mucoadhesive and sustained-release component of buccal tablets. Pharm Dev Tech 4:347–358, 1999.
22. NA Peppas, JJ Sahlin. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int J Pharm 57:169–172, 1989.
23. TF Dillon, RG Douglas, V du Vigneaud, ML Barber. Transbuccal administration of pitocin for induction of labor. Obstet Gynecol 15:587–592, 1960.
24. GW Miller. Induction of labor by buccal administration of oxytocin: review of 50 cases. J Am Osteopath Assoc 72:1110–1113, 1973.

Copyright © 2003 Marcel Dekker, Inc.

25. MY Dawood, O Ylikorkala, F Fuchs. Plasma oxytocin levels and disappearance rate after buccal pitocin. Am J Obstet Gynecol 138:20–24, 1980.
26. M Ishida, Y Machida, N Nambu, T Nagai. New mucosal dosage form of insulin. Chem Pharm Bull 29:810–816, 1981.
27. R Anders, HP Merkle, W Schurr, R Ziegler. Buccal absorption of protirelin: an effective way to stimulate thyrotropin and prolactin. J Pharm Sci 72:1481–1483, 1983.
28. W Schurr, B Knoll, R Ziegler, R Anders, HP Merkle. Comparative study of intravenous, nasal, oral, and buccal TRH administration among healthy subjects. J Endocrinol Invest 8:41–44, 1985.
29. BJ Aungst, NJ Rogers. Site dependence of absorption-promoting actions of laureth-9, Na salicylate, Na_2EDTA, and aprotinin on rectal, nasal, and buccal insulin delivery. Pharm Res 5:305–308, 1988.
30. BJ Aungst, NJ Rogers, E Shefter. Comparison of nasal, rectal, buccal, sublingual and intramuscular insulin efficacy and the effects of a bile salt absorption promoter. J Pharmacol Exp Ther 244:23–27, 1988.
31. Y Nakada, N Awata, C Nakamichi, I Sugimoto. The effect of additives on the oral mucosal absorption of human calcitonin. J Pharmacobio Dyn 11:395–401, 1988.
32. WA Ritschel, GB Ritschel, H Forusz, M Kraeling. Buccal absorption of insulin in the dog. Res Commun Chem Pathol Pharmacol 63:53–67, 1989.
33. NFH Ho, CL Barsuhn. Buccal delivery of drugs. Proc Int Symp Control Rel Bioact Mater 16:24, 1989.
34. CK Oh, WA Ritschel. Biopharmaceutic aspects of buccal absorption of insulin. Methods Find Exp Clin Pharmacol 12:205–212, 1990.
35. GJM Wolany, J Munzer, A Rummelt, HP Merkle. Buccal absorption of sandostatin (octreotide) in conscious beagle dogs. Proc Int Symp Control Rel Bioact Mater 17: 1990 (abstract D341).
36. A al-Achi, R Greenwood. Buccal administration of human insulin in streptozocin-diabetic rats. Res Commun Chem Pathol Pharmacol 82:297–306, 1993.
37. SJ Heiber, CD Ebert, SC Dave, K Smith, SW Kim, D Mix. In vivo buccal delivery of calcitonin. J Control Rel 28:269–270, 1994.
38. D Bayley, C Temple, V Clay, A Steward, N Lowther. The transmucosal absorption of recombinant human interferon-alpha B/D hybrid in the rat and rabbit. J Pharm Pharmacol 47:721–724, 1995.
39. MK Gutniak, H Larsson, SJ Heiber, OT Juneskans, JJ Holst, B Ahren. Potential therapeutic levels of glucagon-like peptide I achieved in humans by a buccal tablet. Diabetes Care 19:843–848, 1996.
40. S Nakane, M Kakumoto, K Yukimatsu, YW Chien. Oral mucosal delivery of LHRH: pharmacokinetic studies of controlled and enhanced transmucosal permeation. Pharm Dev Technol 1:251–259, 1996.
41. AJ Hoogstraate, J Coos Verhoef, A Pijpers, LA van Leengoed, JH Verheijden, HE Junginger, HE Bodde. In vivo buccal delivery of the peptide drug buserelin with glycodeoxycholate as an absorption enhancer in pigs. Pharm Res 13:1233–1237, 1996.
42. C Li, RL Koch, VA Raul, PP Bhatt, TP Johnston. Absorption of thyrotropin releasing

Copyright © 2003 Marcel Dekker, Inc.

hormone in rats using a mucoadhesive buccal patch. Drug Dev Ind Pharm 23:239–246, 1997.
43. C Li, PP Bhatt, TP Johnston. Transmucosal delivery of oxytocin to rabbits using a mucoadhesive buccal patch. Pharm Dev Technol 2:265–274, 1997.
44. HH Alur, JD Beal, SI Pather, AK Mitra, TP Johnston. Evaluation of a novel, natural oligosaccharide gum as a sustained-release and mucoadhesive component of calcitonin buccal tablets. J Pharm Sci 88:1313–1319, 1999.

Copyright © 2003 Marcel Dekker, Inc.

34
Medicated Chewing Gum

Margrethe Rømer Rassing and Jette Jacobsen
The Royal Danish School of Pharmacy, Copenhagen, Denmark

I. INTRODUCTION

Chewing gum has been used worldwide since ancient times when man experienced the pleasure of chewing a variety of substances. Chewing gum can be used as a convenient modified-release drug delivery system. Commercially available medicated chewing gums are currently available for pain relief, smoking cessation, travel illness, and freshening of breath. In addition, a large number of chewing gums intended for prevention of caries, xerostomia alleviation, and vitamin/mineral supplementation are currently available.

Medicated chewing gum offers advantages in comparison to conventional oral mucosal and oral dosage forms both for (a) local treatment of mouth diseases and (b) systemic effect after absorption through the buccal and sublingual mucosa or from the gastrointestinal tract. First, chewing gum can be retained in the oral cavity for long periods. Second, if the drug is readily absorbed across oral mucosa, chewing gum can provide a fast onset time for a systemic effect and the potential for avoidance of gastrointestinal and hepatic first-pass metabolism of susceptible drugs. Finally, chewing gum can be formulated to deliver drugs to the gastrointestinal tract to provide less irritation to the stomach owing to the drug already being dissolved or suspended in saliva when reaching the stomach. Generally, medicated chewing gum has a good stability, the medicine can be taken easily and discretely without the prerequisite of water, and if required, prompt discontinuation of medication is possible.

Several factors affect release of drug from chewing gum including the physicochemical properties of the drug (i.e., aqueous solubility, pK_a value, distribution between gum-saliva), product properties (i.e., composition, mass, manufacturing process), and the process of chewing (i.e., chewing time, chewing rate). The many

Copyright © 2003 Marcel Dekker, Inc.

possibilities for varying the formulations and the manufacturing process make chewing gum a drug delivery system of current interest when rate-controlled drug delivery for an extended period of time is required.

This chapter reviews the fundamentals of medicated chewing gum, historical development, regulatory issues, technologies for modified release, in vitro and in vivo evaluation of drug release, safety aspects, and future developments.

II. HISTORICAL DEVELOPMENT

Gum-like substances, e.g., tree resins, leaves, waxes, and animal skins, have been chewed for many centuries. For a comprehensive review of the history of chewing gum the reader is referred to Hendrickson [1] and Cloys and co-workers [2].

The first commercial chewing gum, "State of Maine pure spruce gum," was marketed in 1848 in the United States. The first patent on chewing gum was filed in 1869. This gum was intended as a dentifrice but it was never marketed [1,3]. In 1928 the first medicated chewing gum, Aspergum®, was commercially introduced. It contained acetylsalicylic acid [4].

The manufacturing processes and components of gums have been developed and improved over the years. Synthetic gum bases were developed during World War II due to shortage of natural gum bases [1]. In the early 1950s artificially sweetened formulations became available [2].

Today, chewing gum as a drug delivery system is commercially available for several drugs, including nicotine, ascorbic acid, sodium fluoride, carbamide, chlorhexidine acetate, zinc salts, and dimenhydrinate.

III. REGULATORY ISSUES

The first monograph on medicated chewing gum was published in the European Pharmacopoeia in 1998. Use of a solid tasteless masticatory gum base and coating, if necessary, to protect from humidity and light, is described. Being a single-dose preparation, medicated chewing gum has to comply with tests for uniformity of content and uniformity of mass. In addition, the microbial quality has to be ensured [5].

Release testing is prescribed to control the bioavailability of the drug(s). In the year 2000 the first monograph on a principle chewing apparatus and a procedure for the determination of drug release from medicated chewing gum was published in the European Pharmacopoeia.

Chewing gum must be chewed to release the drug(s) and it is accepted that a residual of the drug(s) may be left in the chewing gum after finishing chewing. Generally, a reproducible residual of a lipophilic drug will remain after chewing

Copyright © 2003 Marcel Dekker, Inc.

a gum at a constant rate for a predetermined period of time. In some cases, e.g., smoking cessation, one only chews the gum until the desired effect is obtained, hence the expelled gum will contain interindividual variations in the amount of residual drug.

IV. COMPONENTS OF MEDICATED CHEWING GUM

A. Main Components

Medicated chewing gum has a core consisting of the components given in Table 1. The core normally weighs approximately 1 g. A coating can then be applied to the gum either as a film of polymer, wax, or bulk sweetener or as a thicker layer of sugar/sugar alcohol.

The gum base consists of elastomers, resins, fats, emulsifiers, fillers, and possibly antioxidants. There are a number of different commercially available gum bases, each with different characteristics. All gum bases are insoluble in saliva and it is the gum base that determines the basic characteristics of the product. The characteristics that will be influenced by the choice of gum base include texture, release, stability, and the processing. It is possible (but unusual) to manufacture chewing gum with either a larger and a smaller amount of gum base described in Table 1.

B. Taste and Mouthfeel

In contrast to most oral mucosal formulations, chewing gum has a relatively long duration time within the oral cavity. Consequently, sensory parameters are important.

Unpleasant tastes of drugs can vary; e.g., they can be bitter, astringent, or metallic. Because of this there is no general systematic description of methods for taste masking of chewing gum components and it is therefore necessary to rely on experience and cooperate with flavor suppliers.

Table 1 Components of Chewing Gum

Component	Concentration (%)
Drug	Max. approximately 50
Gum base	20–40
Bulk sweeteners	30–75
Softeners	0–10
Flavoring agents	1–5
Coloring agents	<1

Copyright © 2003 Marcel Dekker, Inc.

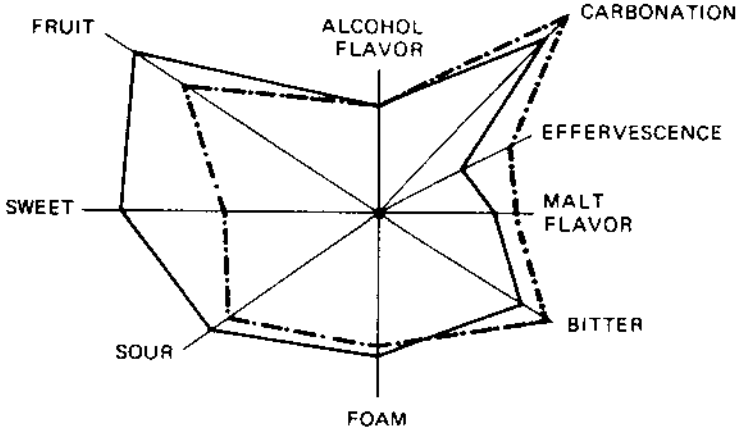


Figure 1 Quantitative descriptive analysis of two competitive chewing gum products; the distance from the center is the mean value for that attribute, and the angles between the outer lines are derived from the correlation coefficients. (——), product 1; (- - - -), product 2. (From Ref. [6].)

To obtain reliable statistical data on the sensory parameters of chewing gum, descriptive sensory analysis parameters are utilized in practice. A few relevant parameters are listed in Figure 1, showing a quantitative descriptive analysis of two competitive products [6]. In general, the parameters are assessed over time, relevant to the treatment period. Fundamental aspects are discussed by Meilgaard and co-workers [7], who describe concepts such as "first bite", "first chew", "chew down", and "residual" as important periods in the product's lifetime in the mouth.

V. MANUFACTURING PROCESS

A. Methods

Chewing gum can be manufactured in different ways. The most common method comprises mixing the gum base with the other ingredients in a mixer with Z-formed blades (Fig. 2). The gum base can either be added in a solid form and softened through heating from the jacket of the mixer or from the frictional heat generated during the mixing process, or it can be added in a melted form. The fact that the texture of the chewing gum has a semifluid dough-like texture during the mixing process and is hardened to a solid unchangeable form after the manufacturing process makes it easy to obtain good homogeneity and there are no segregation problems.

Copyright © 2003 Marcel Dekker, Inc.

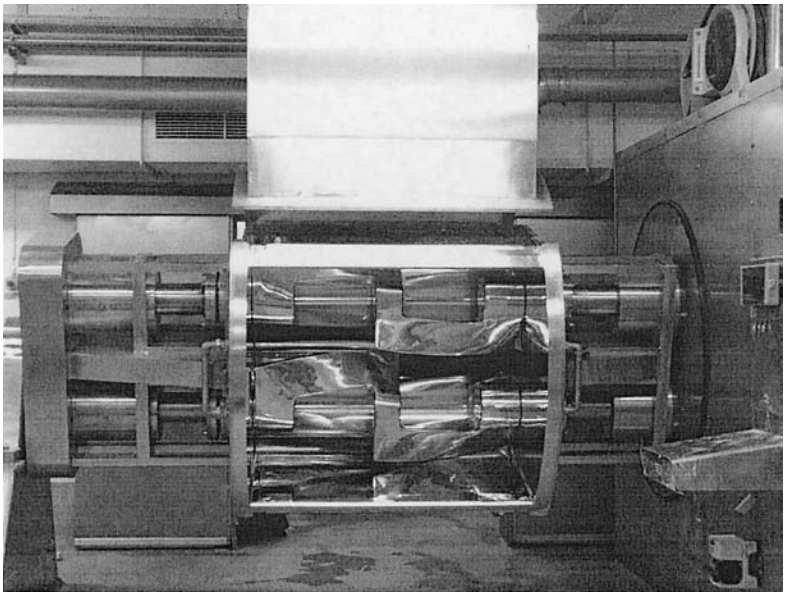


Figure 2 Chewing gum mixer with Z-blades manufactured by Hermann Linden, Maschinenfabrik GmbH & Co KG, Marienhelde, Germany. The working volume of the mixer chamber is 800 L corresponding to approximately 650 kg chewing gum.

Another manufacturing method comprises a continuous production process where the components are added at fixed places in the mixer [8].

In both methods, the chewing gum mass is normally cut into rectangular cores after having been sent through a series of rollers and formed into a thin, wide ribbon. After cooling the cores may be waxed or coated.

Chewing gum can also be manufactured by compression of powders or granulates on a conventional tablet machine (compression technique). The compression technique has the advantage that it is easier to keep different components in the product separated and thereby avoid any potential unwanted chemical interactions. However, products manufactured by the compression technique will normally exhibit poor chewability [9].

B. Scale-Up Problems

By using the traditional manufacturing process using mixing and rolling, the majority of scale-up problems are related to the achievement of a proper texture as this is related to obtaining the proper mass and dimensions of the cores. The

Copyright © 2003 Marcel Dekker, Inc.

problem is solved by choosing the mixer type and size in relation to the adjusting abilities of the full-scale equipment.

During manufacture, because chewing gum softens at temperatures above 30°C, during the coating process temperature can be a problem. If the temperature in the coating equipment is too high it can result in deformation of the gum. It is therefore necessary to coat at a lower temperature.

VI. STABILITY

The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum normally contains little water (2–5%) and the water can be bound to other components in the product and is therefore not very reactive. The water activity (a_w) in chewing gum is normally below 0.6 and typically 0.4–0.5. If the water content is very critical for the stability of a drug, the chewing gum can be manufactured without water (less than 0.2%). This will, however, often make the product hygroscopic and affect the texture.

The low water content also inhibits microbial growth in the chewing gum during storage.

Antioxidants are normally added with the gum base. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packaging.

For very temperature-labile components, e.g., enzymes, the process temperature of 50–60°C during mixing may create a stability problem. It is however, possible to operate the process at a lower temperature to avoid this issue [10].

VII. RELEASE OF DRUGS, SWEETENERS, AND FLAVORS

A. Factors Affecting Release

For products intended for treating disorders in the oral cavity and in the throat as well as for systemic absorption it is often necessary to establish a constant concentration of the drug in the saliva over a longer period of time. From a practical point of view, a realistic release period over which this can be achieved is 0.5–1 h. To obtain a fast systemic effect a release period of 10–15 min is desirable.

The release rate of a drug is determined by a number of factors related to the chewer, the drug, and the chewing gum.

Release from chewing gum can be compared to an extraction process and the chewer-related factors are chewing time, chewing frequency, chewing intensity, and the amount of saliva [11].

Copyright © 2003 Marcel Dekker, Inc.

1. The Drug

The release rate of a drug is first and foremost dependent on the solubility of the drug in water/saliva. Very water-soluble drugs will nearly be completely released from chewing gum in 10–15 min. Drugs with a water solubility of less than 1 g/100 g will exhibit a slow and possibly incomplete release.

Lipid-soluble drugs are dissolved in the lipophilic components of the gum base and thereby slowly and incompletely released. An increase of the gum base percentage decreases the release rate and may increase the residual amount of drug in the gum after chewing.

To obtain an optimal formulation that produces the desired release profile it is nearly always necessary to adjust the release rate of the drug from the gum, either to obtain a slower release of readily water-soluble component or to obtain a faster or more complete release of a water-insoluble component.

2. The Chewing Gum

Several methods are available to modify the release of drugs from chewing gum by modification of the gum base.

Nicotine has been formulated as a complex bound to a cation exchange resin, e.g., divinylbenzenemethacrylic acid or styrene-divinylbenzene. A higher percentage of ion exchange gives a slower release rate [12]. The ion exchange principle could also be used for other ionic drugs.

An alternative method to increase the release of a lipophilic drug is to produce a hydrophilic cyclodextrin complex [13,14].

It has been shown that the release rate from chewing gum can also be influenced by encapsulation of the drug. A general description of encapsulation techniques for modified release from chewing gum is given in the patent literature (e.g., Ref. [15]). One method comprises a hydrophilic or a hydrophobic coating of particles of the drug, normally by spray coating. To reduce the release rate a coating with ethyl cellulose can be used [16].

Other methods to modify release of drugs from chewing gum comprise granulation of the drug with hydrophilic components/melted lipids or by mixing the drug with a melted polymer [17]. In addition, flavor oils can be adsorbed to organic or inorganic carriers, e.g., polymer gum base [18] components or silica [19,20], and thereby prolong the release.

Solubilization can be used as a method to increase the release of sparingly water-soluble drugs by adding emulsifying components. However, a problem with this technique is that it has a softening or dissolving effect on the gum base. This requires a special gum base [21].

For further examples of principles for effecting drug release from chewing gum see the reviews by Rassing [11,22].

Copyright © 2003 Marcel Dekker, Inc.

B. Release Methods and Requirements

In vitro release methods mimicking in vivo release are a desirable prerequisite for development of chewing gum formulations as drug delivery systems.

Previous in vitro methodologies and apparatuses for assessing drug release from medicated chewing gum have been reviewed by Rassing [11,22]. Recently a new chewing apparatus has been reported that kneads the whole gum uniformly [23]. Requirements of appropriate release of drug(s) are determined for each individual product according to the therapeutic needs on a case-by-case basis.

C. In Vitro/In Vivo Correlation

A few studies have been reported concerning in vitro/in vivo release correlations. In one study, chewing gums containing 30 mg of urea were chewed for different periods of time up to 30 min. A chewing method similar to the method described in the European Pharmacopoeia was used for the in vitro release experiment. Volunteers chewed the gums and the residual amount of urea in the gum was analyzed to determine the in vivo release profile. A linear in vitro/in vivo correlation was obtained; $r = 0.9992$ (see Fig. 3 [24]).

In another study, using the same in vitro and in vivo release methods described above, four different chewing gum formulations containing the water-soluble drug ascorbic acid were evaluated. The correlation between the in vitro

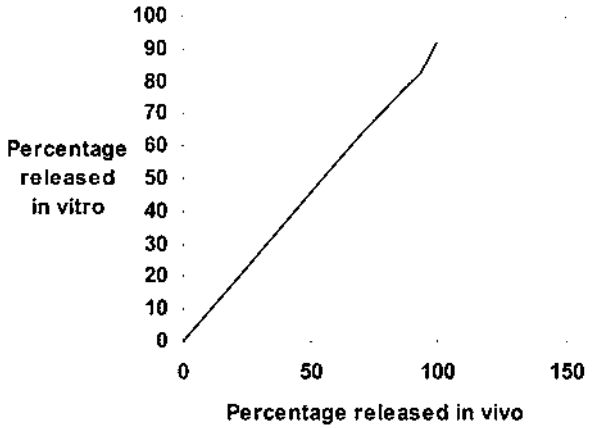


Figure 3 Correlation between the in vitro and in vivo release of urea from chewing gum within 30 min of chewing. (From Ref. [24].)

Copyright © 2003 Marcel Dekker, Inc.

and in vivo release profiles was linear within the first 5 min and between 5 and 15 min [25].

The in vitro and in vivo release of the poorly water-soluble drug, miconazole, from four different chewing gums has also been reported [26]. The in vitro release method was according to the European Pharmacopoeia. However, for the in vivo study the gums were chewed for 30 min, and saliva samples collected at regular time intervals [26]. The in vitro release profiles correlated well with the in vivo release profiles. The in vivo release resulted in therapeutically active concentrations of miconazole in saliva.

VIII. SAFETY ASPECTS

Generally, today it is perfectly safe to chew a gum. Previously, hard chewing gums have caused broken teeth. Extensive chewing for a long period of time may cause painful jaw muscles, and extensive use of sugar-alcohol-containing chewing gum may cause diarrhea. Long-term frequent chewing of gums has been reported to cause increased release of mercury vapor from dental amalgam fillings [27,28]. However, medicated chewing gum does not normally require extensive chewing, or consumption to a great extent.

Flavors, colors, etc. may cause allergic reactions.

Overdosing by use of chewing gum is unlikely because a large amount of gum has to be chewed in a short period of time to achieve this. Swallowing pieces of medicated chewing gum will only cause minor release of the drug because the drug can only be released from the gum base by active chewing.

As a general rule, medicated chewing gum (like other medicines) should be kept out of reach of children. In addition, if required, drug delivery may be promptly terminated by removal of the gum.

IX. FUTURE DEVELOPMENTS

Chewing gum of the future will most likely be composed in a way so it can be removed from indoor and outdoor surfaces by conventional cleaning methods and technologies. It will disappear by means of nature's own remedies i.e., water, light, and bacteria.

In the future chewing gum as a drug delivery system will likely be forthcoming for the treatment of mouth and throat diseases, both of which require a long period of local drug release to the oral cavity.

By using optimal release systems and a better utilization of flavors, more drugs will be successfully formulated in chewing gum in the future.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. R Hendrickson. The Great American Chewing Gum Book. 1st ed. Radnor, PA: Clinton Book Company, 1976.
2. LA Cloys, AG Christensen, JA Christensen. The development and history of chewing gum. Bull Hist Dent 40:57–65, 1992.
3. Anonymous. A concise history of chewing gum. Dent Stud Mag 47:626–644, 1969.
4. Growth through research: a history of Schering-Plough Corporation. Corporation brochure. 1992, pp. 3, 6.
5. Council of Europe. European Pharmacopoeia. 4th ed. Strasbourg: European Directorate for the Quality of Medicines, 2001, pp. 537–538.
6. H Stone, J Sidel, S Oliver, A Woolsey, RC Singleton. Sensory evaluation by quantitative descriptive analysis. Food Technol 28:24–32, 1974.
7. M Meilgaard, GV Civille, BT Carr. Sensory Evaluation Techniques. 2nd ed. Boca Raton, FL: CRC Press. 1991, pp. 162–169.
8. KB Broderick, DJ Townsend, DW Record, JH Song, PG Schnell, CE Sundstrom. Continuous chewing gum manufacturing process yielding gum with improved flavor perception. EP 0763330, 1995.
9. G Gergely, T Gergely, I Gergely. Chewing gum and production method thereof. US patent 4,737,366, 1986.
10. US Angel. Chewing gum and process for manufacture thereof. EP 2078186, 1994.
11. MR Rassing. Specialized oral mucosal drug delivery systems: chewing gum. In: MJ Rathbone, ed. Oral Mucosal Drug Delivery. New York: Marcel Dekker, 1996, pp. 319–357.
12. S Lichtneckert, C Lundgren, O Ferno. Chewable smoking substitute composition. US patent 3,901,248, 1974.
13. J Jacobsen, S Bjerregaard, M Pedersen. Cyclodextrin inclusion complexes of antimycotics intended to act in the oral cavity: drug supersaturation, toxicity on TR146 cells and release from a delivery system. Eur J Pharm Biopharm 48:217–224, 1999.
14. J Szejtli, S Pütter. Chewing gum compositions. EP 0575 977, 1993.
15. GN McGrew, DG Barkalow, SS Johnson, DW Record, MM Patel, JD Nimz, SE Zibell, RJ Yatka, MJ Greenberg, RA Aumann, DJ Zyck, DJ Sitler, JS Hook, JR Maxwell, MA Reed, VV Gudas, PG Schnell, HT Tyrpin, MP Russell, DL Witkewitz, JH Song, DJ Townsend, DA Seielstad. Chewing gum containing medicament active agents. WO 00/35298A1, 1999.
16. AM Morella, S Lukas. Microcapsule composition and process. CA 2068366, 1992.
17. RK Yang. Encapsulation composition for use with chewing gum and edible products. US patent 4,740,376, 1987.
18. RP D'Amelia, TR Cea, JE Beam, RA, White, SC Agro. Chewing gum containing flavorant adsorbed in cross-linked elastomeric polymer. US patent 5,458,891, 1994.
19. JH Song, SB Courtright. Flavor releasing structures for chewing gum. US patent 5,128,155, 1990.
20. W Bell, TJ Carroll. Chewing gum or confection containing flavorant adsorbed on silica. US patent 5,338,809, 1993.

Copyright © 2003 Marcel Dekker, Inc.

21. C Andersen, M Pedersen. Chewing gum composition with accelerated, controlled release of active agents. EP 486563, 1990.
22. MR Rassing. Chewing gum as a drug delivery system. Adv Drug Del Rev 13:89–121, 1994.
23. C Kvist, SB Andersson, S Fors, B Wennergren, J Berglund. Apparatus for studying in vitro drug release from medicated chewing gums. Int J Pharm 189:57–65, 1999.
24. P Martinsen. Ureas enhancereffekt på permeation over cellekulturen TR146 og release fra V6® tyggegummi samt β-lupeols permeation over cellekulturen. Master's thesis, The Royal Danish School of Pharmacy, Copenhagen, 1998.
25. LL Christrup, N Møller. Chewing gum as a drug delivery system. Arch Pharm Chem Sci Ed 14:30–36, 1986.
26. M Pedersen, MR Rassing. Miconazole chewing gum as a drug delivery system: application of solid dispersion technique and lecithin. Drug Dev Ind Pharm 16:2015–2030, 1990.
27. G Sallstan, J Thoren, L Barrefard, A Schutz, G Skarping. Long-term use of nicotine chewing gum and mercury exposure from dental amalgam fillings. J Dent Res 75: 594–598, 1996.
28. JR Mackert, A Berglund. Mercury exposure from dental amalgam fillings: absorbed dose and the potential for adverse health effects. Crit Rev Oral Biol Med 8:410–436, 1997.

Copyright © 2003 Marcel Dekker, Inc.

35

Immediate-Immediate Release (I^2R) Lingual or Buccal Spray Formulations for Transmucosal Delivery of Drug Substances

Harry A. Dugger III, Kenneth E. Cleaver, and Donald P. Cox
Flemington Pharmaceutical Corporation, Flemington, New Jersey, U.S.A.

I. INTRODUCTION

Mucosal delivery of drugs has been reviewed [1,2] extensively mainly from a sustained-delivery point of view using buccal patches, mucoadhesives, and other means for delivery to prolong the contact of the substance to be absorbed with the mucosal membrane. Immediate-immediate release (I^2R™) lingual or buccal spray technology, which is the subject of this chapter, is quite different from these other methods in that these formulations do not require these means to prolong contact with the buccal mucosa. The term "immediate-immediate release" is used because these formulations enable the drug to reach the systemic circulation faster than standard immediate-release tablets, capsules, and other oral formulations. The formulations employed for these purposes are usually designated either as lingual sprays or buccal sprays but in this chapter the term "lingual sprays" will be used throughout.

Oral lingual sprays are sprayed directly into the oral cavity onto the tongue and buccal tissue. The drug substance is transported in part through the oral mucosa directly into the bloodstream. Since less drug travels through the gastrointestinal tract, the loss due to the first-pass effect (metabolism by the liver during the absorption phase) is reduced. Because of the rapid delivery of drug into the systemic circulation, for the first time an oral route may accomplish the immediate treatment of symptoms using dosing-as-needed regimens. In some cases the

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Unique Advantages of Oral Lingual Spray

Characteristic	Oral lingual spray	Nasal spray	Fast-dissolve tablets	Buccal patches	Inhalers
Rapid blood levels	Yes	Maybe	No	Maybe	Maybe
High bioavailability	Yes	No	No	Probably	No
Avoids first-pass effect	Yes	No	No	Yes	Maybe
Lower dosing	Yes	No	No	Maybe	No
Long-term stability	Yes	Maybe	Yes	Yes	Maybe

drug must be given in large quantities because the first-pass metabolism will remove most of the drug before it reaches systemic circulation. Lingual sprays, which avoid the first-pass effect, allow using much smaller doses, and achieve the same therapeutic effect. The lower dose is most important where metabolism leads to reactive intermediates that can bind to DNA and/or RNA. Cavalieri [3] has proposed just such a metabolite to explain the carcinogenic potential of estradiol and estrone. Hence, I^2R delivery puts an active therapeutic agent into the bloodstream, safely and rapidly, without the use of invasive techniques. Table 1 compares I^2R formulations with some other technologies currently being used to attempt fast delivery at a lower dose.

II. CURRENT APPLICATIONS

Nitroglycerin lingual spray (marketed as Nitrolingual® Spray in the United States) was the first commercially successful lingual spray product. Lingual sprays of other nitrate esters, such as isosorbide dinitrate and mononitrate, have also been reported, but because of the larger dose required these lingual sprays were not as medically interesting as the nitroglycerin lingual spray. Patents [4–8] in this area and published literature [9] indicate that lingual absorption of nitroglycerin was very fast with a maximum plasma level concentration (C_{max}) being reached in 5–8 min with an equally fast decline in these levels over a period of 30 min. Two possible explanations for this rapid rise and equally rapid decline in plasma levels are:

1. The time for penetration of the mucosal membrane was very short before the nitroglycerin was cleared from the mouth by swallowing, and/or
2. Nitroglycerin was removed in part by degradation or metabolism.

Copyright © 2003 Marcel Dekker, Inc.

The relative amounts of drug removed by the two mechanisms could vary depending on the drug substance being delivered. Several other patents describing lingual sprays for analgesics [10], caffeine [11], nicotine [12,13], nifedipine [14], verapamil and gallopamil [15], and a patent covering the use of 1,1,1,2,3,3,3-heptafluoropropane as a propellant [16] have been published or issued but they were not accompanied by enough clinical data to allow judgments to be made as to which of the two pathways was operative. To our knowledge none of the products in those patents have been registered for marketing in any country.

If the first explanation was correct, then one would expect that other drugs that did not have the rapid penetrating properties of nitroglycerin and low molecular weight would not have enough time for absorption before they were cleared. Therefore, lingual sprays containing these drugs could not deliver a therapeutically meaningful amount in the time before clearance from the oral cavity. If the second explanation was correct and removal by degradation is a major pathway of clearance for nitroglycerin, then other drugs that were not as rapidly degraded might still have enough time prior to clearance for a therapeutically meaning amount to be absorbed. The I^2R formulations were developed to explore which of these two possible explanations could be correct and for which products they may apply.

III. IMMEDIATE-IMMEDIATE RELEASE (I^2R) FORMULATIONS

A. Manufacture

In the simplest terms these formulations are solutions of the drug substance in either a polar [17] or nonpolar [18] solvent delivered by means of a pump aerosol spray or a propellant-driven aerosol spray into the oral cavity. The manufacture of these formulations involves dissolving the drug substance plus other excipients such as flavors in a suitable solvent and placing this solution in a bottle or canister. A suitable metered-dose valve is attached to the bottle or canister. If a propellant is used, it is added through the valve after attachment of the valve. In-process controls involve assay to assure homogeneity of the solution prior to filling the bottle or canister. Particle size, dissolution testing, and other such factors of concern for tablets and other solid dosage forms are not applicable.

B. Clinical Results

A series of formulations have been prepared and tested in pharmacokinetic studies comparing them with the standard oral treatment or in pharmacodynamic studies comparing the therapeutic effects against the standard therapy. The following are the results of some of these studies.

Copyright © 2003 Marcel Dekker, Inc.

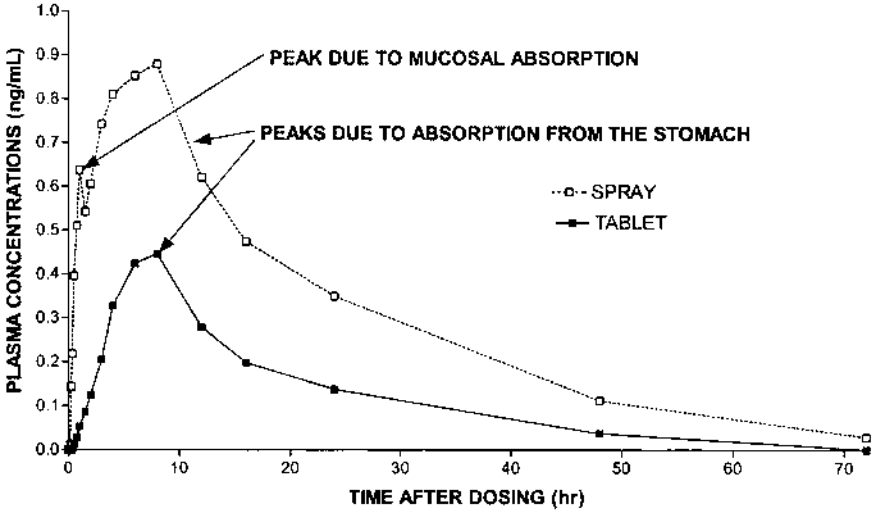


Figure 1 Mean plasma levels of clemastine after administration of a clemastine lingual spray (2 × 1.34 mg) and a Tavist tablet (2.68 mg) ($n = 8$).

1. Clemastine Fumarate Lingual Spray

A pharmacokinetic study was carried out comparing a clemastine fumarate oral tablet (2.68 mg) manufactured by Novartis Pharmaceuticals Corp. (Tavist®) with two activations of a lingual spray delivering 1.34 mg/dose. The mean 72-h plasma levels show two peaks for the lingual spray and one for the tablet (Fig. 1). The first peak in the mean plasma level curve after administration of the lingual spray is attributed to absorption through the oral mucosa and the second, which is similar to the mean plasma curve obtained after administration of the tablet, is attributed to absorption from the gastrointestinal tract (GI tract). The clemastine that was not absorbed through the oral mucosa would be swallowed and absorbed from the GI tract. Figure 2 shows the first 90 min of the total 72-h curve in Figure 1. The lingual spray delivers significant amounts of the drug within 5–10 min and the first peak is reached within 63 min (the lingual spray curve is off-scale after 10 min) whereas the tablet only starts to deliver clemastine to the systemic circulation sometime between 20 and 30 min after administration.

The mean time-to-maximum-plasma-level (T_{max}) of the tablet was 7.0 h. Just as the rate of mucosal absorption begins to decline, the absorption from the GI tract begins and builds on the plasma levels obtained by the mucosal absorption. Based on comparisons of the mean area-under-the-curve (AUC), the combined mucosal/GI absorption is 4.89 times larger than absorption after adminis-

Copyright © 2003 Marcel Dekker, Inc.

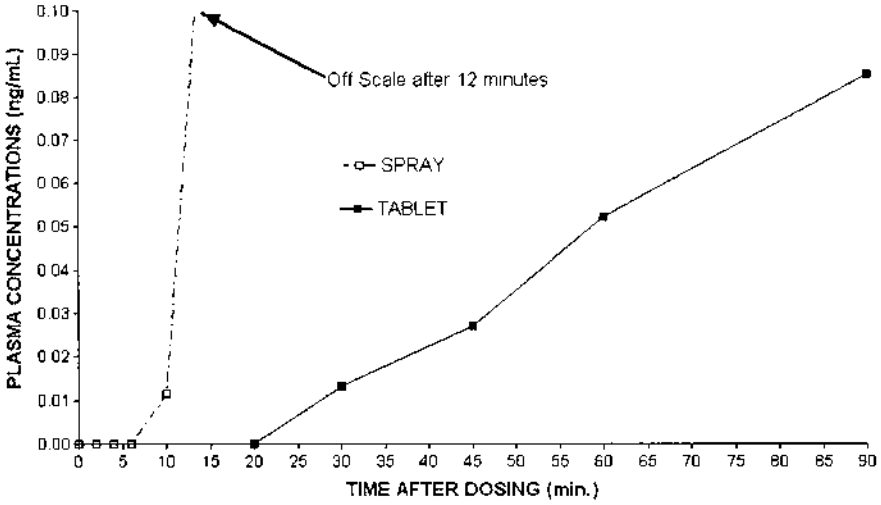


Figure 2 Mean plasma levels of clemastine after administration of a clemastine lingual spray (2 × 1.34 mg) and a Tavist tablet (2.68 mg) ($n = 8$).

tration of the tablet. Since the duration of the therapeutic effect is dependent on the rate of elimination and not on the rate of absorption, both formulations should be effective over the same period of time. The half-life of elimination for the spray (15 h), though slightly larger, is not significantly different from that of the tablet (11 h). Table 2 summarizes the observed pharmacokinetic parameters.

2. Estradiol Lingual Spray

A pharmacokinetic study was carried out comparing the plasma levels obtained after administration of an Estrace® tablet (2.0 mg) manufactured by Bristol-Meyers Squibb Co. and a lingual spray delivering 2.0 mg of estradiol in a single activation. Figure 3 shows the relationship of the plasma levels obtained after administration of the tablet with the levels obtained after administration of the lingual spray. The spray achieved a mean C_{max} 75.8 (Table 2) times higher than the tablet with a mean T_{max} of 42 min whereas the mean T_{max} of the tablet was observed at 8.33 h (Table 2). The mean AUC after the administration of the lingual spray was 9.6 times larger (Table 2) than the mean AUC after administration of the tablet. The plasma concentrations of estradiol and estrone obtained for the I²R formulation and the tablet, respectively, are shown in Figures 4 and 5.

These figures show the effect of first-pass metabolism on the absorption

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Clemastine Pharmacokinetic Parameters After Administration of a Clemastine Fumarate Lingual Spray (2 × 1.34 mg) and a Tavist Tablet (2.68 mg) (n = 8)

	AUC (0–72 h) (ng/mL/h)			T_{max} (last peak)[a] (h)			C_{max} (last peak)[a] (ng/mL)		
	Spray LS	Tablet	Ratio LS/T	Spray LS	Tablet	Ratio LS/T	Spray LS	Tablet	Ratio LS/T
Mean	20.99	7.57	4.89[b]	7.00	7.0	1.05	0.81	0.350	3.64
Standard error	1.88	1.74	2.36	0.68	0.72	0.056	0.128	0.078	1.58
Median	19.49	6.89	2.44	8.00	8.0	1	0.83	0.332	2.02
Standard deviation	4.61	4.62	5.78	1.67	1.91	0.136	0.313	0.206	3.88

[a] In the plasma curve of the lingual spray an additional peak was observed at a mean T_{max} of 1.0 h with a mean C_{max} of 0.64 ng/mL.
[b] Mean of the ratios.

Copyright © 2003 Marcel Dekker, Inc.

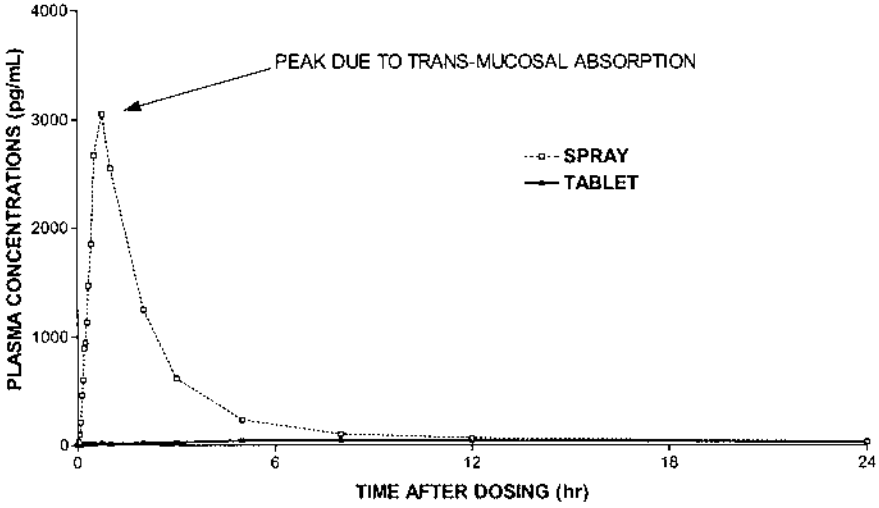


Figure 3 Mean plasma levels of 17-beta-estradiol after administration of a lingual spray (2.0 mg) and a Estrace tablet (2.0 mg) ($n = 6$).

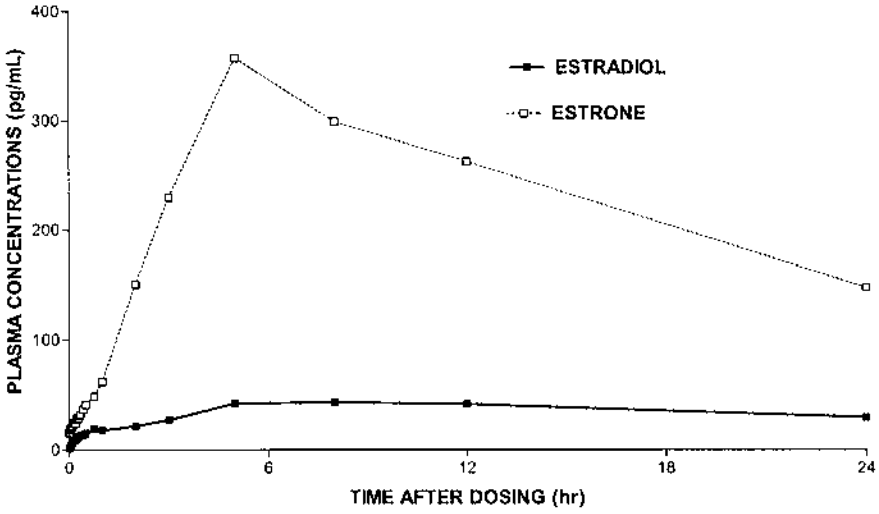


Figure 4 Mean plasma levels of 17-beta-estradiol and estrone after administration of a Estrace tablet (2.0 mg) ($n = 6$).

Copyright © 2003 Marcel Dekker, Inc.

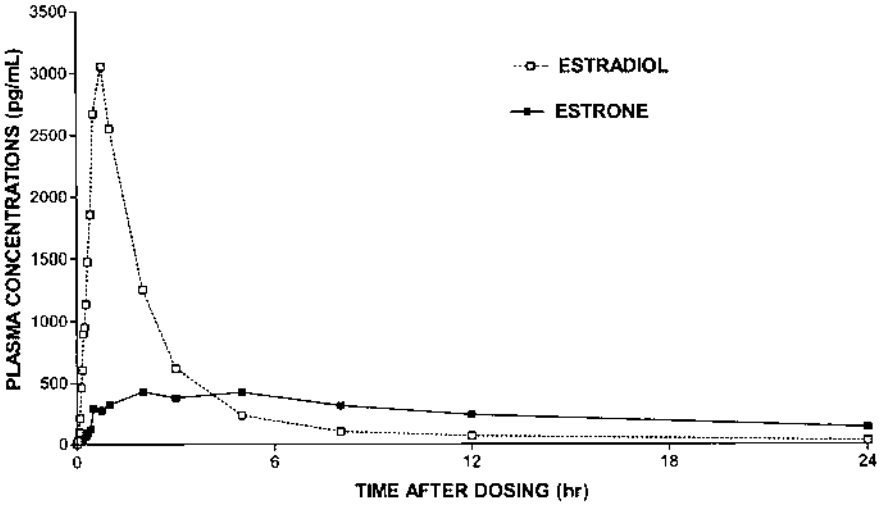


Figure 5 Mean plasma levels of 17-beta-estradiol and estrone after administration of a lingual spray (2.0 mg) ($n = 6$).

of estradiol. The most abundant entity in the plasma after administration of the tablet (Fig. 4) is the metabolite estrone (estradiol/estrone: 1.0:6.25) while the most abundant entity after administration of the I^2R formulation is estradiol (Fig. 5) (estradiol/estrone: 1.0:0.88). Figure 6 displays the relative amounts of estrone obtained after administration of the tablet and the spray. The amount of estrone in systemic circulation is about the same in terms of AUC (I^2R/tablet: 1.28:1.0) as expected, since the estradiol would be eventually metabolized to estrone, if not on the first pass through the liver, then on other passes or in the target tissues. Tables 3 and 4 summarize the pharmacokinetic parameters obtained for estradiol and estrone, respectively.

3. Progesterone

Once the results of the estradiol study were available, the pharmacokinetic study comparing a 100-mg Prometrium® capsule with an I^2R formulation containing progesterone had to be designed differently than the estradiol lingual spray study. If a 100-mg I^2R formulation containing progesterone would deliver a mean C_{max} 70 times higher than the capsule, a distinct possibility existed that very high plasma levels would be reached that could lead to side effects. Therefore, to produce blood levels approximately equivalent to the Prometrium capsule, an I^2R formulation delivering a lower dose was developed to compensate for the expected greater efficiency in progesterone lingual spray delivery.

Copyright © 2003 Marcel Dekker, Inc.

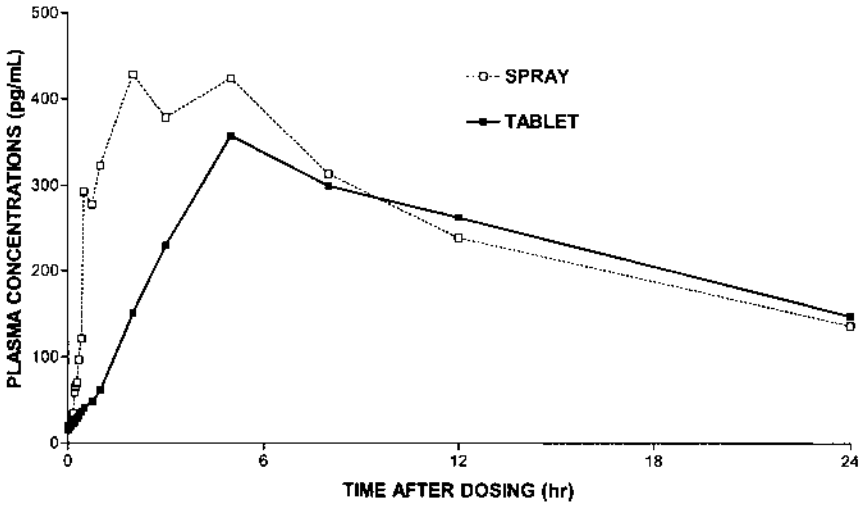


Figure 6 Mean plasma levels of estrone after administration of a lingual spray (2.0 mg) and a Estrace tablet (2.0 mg) ($n = 6$).

The study employed the Prometrium capsule delivering 100 mg of progesterone and I²R formulation delivering only 2.0 mg of progesterone. The results of this study are shown in Figure 7. The plasma levels after administration of the Prometrium capsule, as measured by radioimmuno assay (RIA), were highly variable. A mean C_{max} was reached only at a mean T_{max} of 2.25 h, while the mean T_{max} obtained after administration of the lingual spray was 32.3 min. The ratio of the AUCs after administration of the I²R formulation to that obtained after administration of the capsule was 0.43, indicating that on a per-milligram-dosed basis the lingual spray delivered 21.4 times more progesterone to the systemic circulation than the capsule and with much less variability. The pharmacokinetic parameters obtained are summarized in Table 5.

IV. DISCUSSION

The results of the above studies demonstrate that nitroglycerin lingual sprays were not unique in their ability to deliver the drug substance through the oral mucosa efficiently in therapeutically meaningful amounts. In fact, with I²R formulations studied to date, the absorption rate starts to decrease in about 30–60 min. This decrease could be due to a decrease in the fraction of the drug available for absorption because of absorption, or due to clearing of the mouth by swal-

Copyright © 2003 Marcel Dekker, Inc.

Table 3 Estradiol Pharmacokinetic Parameters After Administration of an Estradiol Lingual Spray (2.0 mg) and an Estrace Tablet (2.0 mg) ($n = 6$)

	AUC (0–24 h) (pg/mL/h)			T_{max} (h)			C_{max} (pg/mL)		
	Spray LS	Tablet	Ratio LS/T	Spray LS	Tablet	Ratio LS/T	Spray LS	Tablet	Ratio LS/T
Mean	7769	856	9.6	0.71	8.33	0.10	3322	47.4	75.8
Standard error	1493	141	0.8	0.08	1.28	0.01	524	8.7	7.7
Median	7827	826	9.0	0.75	8.00	0.10	3215	45.5	76.5
Standard deviation	3658	344	1.9	0.19	3.14	0.02	1285	21.3	17.3

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Estrone Pharmacokinetic Parameters After Administration of an Estradiol Lingual Spray (2.0 mg) and an Estrace Tablet (2.0 mg) ($n = 6$)

	AUC (0–24 h) (pg/mL/h)			T_{max} (h)			C_{max} (pg/mL)		
	Spray LS	Tablet	Ratio LS/T	Spray LS	Tablet	Ratio LS/T	Spray LS	Tablet	Ratio LS/T
Mean	6777	5275	1.28	2.25	6.17	0.45	505.00	368.50	1.53
Standard error	620	600	0.10	0.66	1.17	0.17	59.55	58.17	0.23
Median	6898	5352	1.33	2.00	5.00	0.40	488.00	354.50	1.63
Standard deviation	1518	1469	.022	1.60	2.86	0.37	145.87	142.50	0.51

Copyright © 2003 Marcel Dekker, Inc.

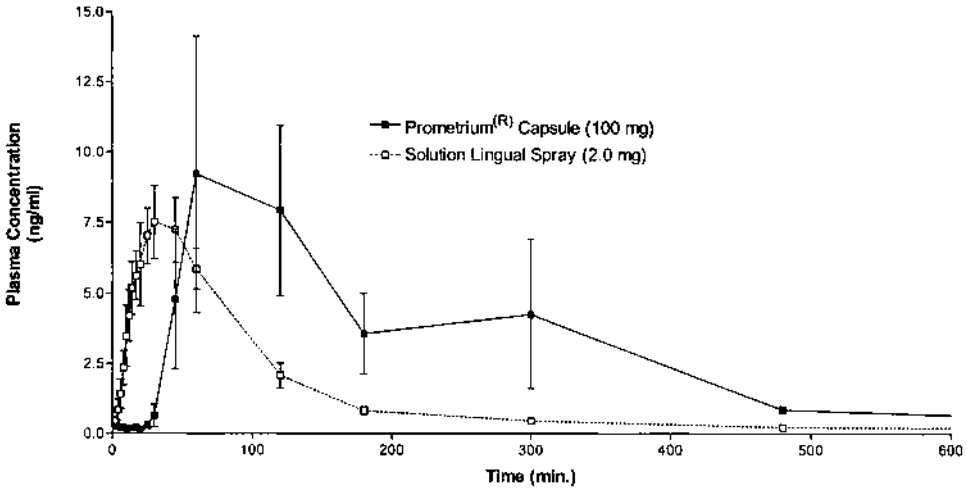


Figure 7 Mean plasma levels of progesterone after administration of a progesterone lingual spray (2.0 mg) and a Prometrium capsule (100.0 mg) ($n = 4$).

lowing, or both. In the case of clemastine, clearing of the mouth is certainly playing a role as seen in the large wave of clemastine arriving in the plasma at the later time periods by absorption from the GI tract. In the case of estradiol and progesterone, it is more difficult to see this GI absorption because of the larger first-pass effect experienced by these two drugs. The more lipophilic the drug substance, the larger is the amount that will be absorbed through the mucosal membrane relative to the standard immediate-release formulation. Clemastine fumarate is an amine salt with some solubility in water and solubility in alcohol whereas estradiol and progesterone are completely insoluble in water.

The most plausible series of events to explain the absorption process and the apparent limit of about 30–60 min for the absorption phase is the following:

1. The lingual spray delivers a mist of fine droplets onto the mucosal membrane, probably onto the mucin layer.
2. The solvent either is absorbed through the membrane possibly taking some of the drug substance with it or it is diluted by the saliva or both.
3. The drug substance that was in the solvent and was not immediately absorbed is deposited as a thin film onto the mucin layer covering the membrane [2], which probably acts as a natural mucoadhesive and binds the drug to the membrane.
4. The drug substance can then diffuse into the lipid layer in the membrane [6] and from there into the systemic circulation.

Copyright © 2003 Marcel Dekker, Inc.

Table 5 Progesterone Pharmacokinetic Parameters After Administration of a Progesterone Lingual Spray (2.0 mg) and a Prometrium Capsule (100.0 mg) ($n = 4$)

	AUC (0–24 h) (ng/mL/h)			T_{max} (min)			C_{max} (ng/mL)		
	Spray LS	Capsule	Ratio LS/T	Spray LS	Capsule	Ratio LS/T	Spray LS	Capsule	Ratio LS/T
Mean	1005.8	2408.3	0.43	32.5	135.0	0.40	7.87	13.6	0.62
Standard error	134.8	226.1	0.06	4.3	56.8	0.15	1.25	2.9	0.12
Median	1077.5	2262.5	0.46	30.0	90.0	0.38	7.99	11.8	0.59
Standard deviation	269.6	452.2	0.12	8.7	113.6	0.29	2.49	5.9	0.24

Copyright © 2003 Marcel Dekker, Inc.

5. Alternatively, the drug can dissolve in the saliva and be transported into the stomach on swallowing, or as the mucin layer is sloughed off and replaced by new material, the drug can be transported with the sloughed layer into the stomach.

The principle that equal plasma levels give equal therapeutic results is the basis of all generic drug approvals for solid oral-dosage forms that give a blood level. When plasma level curves parallel each other, one can also conclude that the time profile of the therapeutic effect will also be the same. If the profiles are different, then the timing of the therapeutic effect will also be different. Based on these principles and the results of the above studies, one would predict that the amount dosed could be reduced by as much as threefold in the case of clemastine, 10-fold in the case of estradiol, and 20-fold in the case of progesterone while still having the same efficacy. One might also expect that the lingual sprays would have a faster onset of therapeutic effect as a result of the very fast rise in plasma levels. These possibilities are being investigated at present.

V. SUMMARY

Like sustained-release formulations, I^2R oral dosage forms will allow new indications and breathe new life into existing therapies. For example, conventional oral drugs often are used in maintenance dosing regimens because the time to onset of a therapeutic effect is long. With this lag in therapeutic effect, the patient would often rather use a maintenance program with the concurrent exposure to unnecessary amounts of drug substance than risk suffering symptoms for hours while waiting for relief.

I^2R formulations may allow rapid, dosing-as-needed treatments (PRN dosing) because fast onset would be the rule rather than the exception. I^2R formulations will avoid the first-pass effect, bypassing the liver for that fraction of the drug absorbed transmucosally and allowing one to use much smaller doses and achieve the same therapeutic effect. As noted above, the lower dose is most important where metabolism leads to reactive intermediates that can bind irreversibly to DNA and/or RNA or other body components. The I^2R formulations also lend themselves to the development of more convenient drug therapies for geriatric and pediatric patients as well as treatments for patients who are not able to take solid medications by mouth.

Some examples of candidate compounds suited for lingual spray application on the basis of the need for fast treatment or relief of symptoms and/or the ability to deliver the same therapeutic effect with a lower dose are antihistamines, steroid hormones, antidepressants, sedatives, and the like (see Table 6).

Copyright © 2003 Marcel Dekker, Inc.

Table 6 Some Examples of Drugs Where Fast Onset and/or Lower Dose Would Be Important

Antihistamines	Cardiovascular agents
Clemastine	Nitrates (nitroglycerin)
Chlorpheniramine	ACE inhibitors
Dexchlorpheniramine	Calcium antagonists
Loratadine	Beta-blockers
Antidepressants	Sedatives
Fluoxetine (Prozac)	Barbiturates
Buspirone (Buspar)	Benzodiazepines
Biologically active amines	Steroids
Bromocriptine	Testosterone
Apomorphine	Estradiol
Selegiline	Progesterone
Amitriptyline	Combinations of the above
Dopamine precursors	Antinauseants
Serotonin precursors	Prochlorperazine
Peptides	Chlorpromazine
Cyclosporine	Perphenazine
Insulin	Decongestants
Calcitonin	Dextromethorphan
Anorexiants	Pseudoephedrine
Dextroamphetamine	Nutritionals
Phentermine	Vitamins
Mazindol	Calcium supplements
Sibutramine	Iron supplements
Sleep inducers	
Temazepam	
Doxylamine	
Zolpidem	
Triazolam	
Nitrazepam	

REFERENCES

1. MJ Rathbone. Oral Mucosal Drug Delivery. New York: Marcel Dekker, 1996.
2. AH Shojaei. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Sci 1:15–30, 1998.
3. EL Cavalieri. Molecular origin of cancer: catechol estrogem-3,4-quinones as endogenous tumor initiators. Proc Natl Acad Sci USA 94:10937–10942, 1997.
4. G Egis. Nitroglycerinhaltige treibgasfreie Aerosolpräparate und Verfahren zu deren Herstellung. DE patent 3922 650 A1, 1990.

Copyright © 2003 Marcel Dekker, Inc.

5. W Cholcha. Nitroglycerin-pumpspray. DE patent 4007 705 C1, 1991.
6. K Klokkers-Bethke. Nitroglycerinhaltiger, hydrophiler, wässriger pumpspray. EU patent 0471 969 A1, 1991.
7. I Bonnacker. Pharmazeutische spray-zubereitungen mit coronaraktiven wirkstoffen. DE patent 4038 203 A1, 1992.
8. E Silson, J Francos. Composition pour áerosols utilisable pour soulager la douleur accompagnant l'angine de poitrine. FR patent FR-A-2735, 1964.
9. PM Dewkand, T Tanner, AJ Woodward. Die bioverfügbarkeit von nitroglycerin-sprays als voraussetzung für äquivalente dosierung beim kardialen notfall. Herz Gefässe 536–544, 1987.
10. JA Deihl. Sprayable analgesic composition and method of use. WO patent 94/13280, 1994.
11. JE Spector. Method for oral spray administration of caffeine. US patent 5,456,677, 1995.
12. J von Wielligh. Product for assisting a smoker in giving-up the habit. EU patent 0 557 129 A1, 1993.
13. R Baker, G Santus, S Vintilla-Friedman. Method and therapeutic system for smoking cessation. US patent 5.593,684, 1997.
14. A Hegasy, K Rämsch. Dihydropyridinspray, verfahren su seiner herstellung and seine pharmazeutische verwendung. DE patent 3544 692 A1, 1987.
15. K Fömming, G Neugebauer, N Rietbrock, B Woodcock. Verapamil and gallopamil und ihre physiologisch verträglichen salze zur resorptiven anwendung auf schleimhäuten des mundes, des nasen-rachen-räums und des rektums. DE patent 3338 978 A1, 1984.
16. J Fassberg, J Sequeira, M Kopcha. Non-chlorofluorocarbon aerosol formulations. US patent 5,474,759, 1995.
17. H Dugger. Buccal polar spray or capsule. US patent 6,110,486, 2000.
18. H Dugger. Buccal non polar spray or capsule. US patent 5,955,098, 1999.

Copyright © 2003 Marcel Dekker, Inc.

36

Liquid Crystalline Phases of Glyceryl Mono-oleate as Oral Mucosal Drug Delivery Systems

Jaehwi Lee
School of Pharmacy, Purdue University, West Lafayette, Indiana, U.S.A.

Ian W. Kellaway
School of Pharmacy, University of London, London, England

I. INTRODUCTION

Development of new drug delivery systems often requires a suitable material that is safe and can efficiently deliver drugs with various physicochemical properties. In this regard, glyceryl mono-oleate (GMO) and its liquid crystalline phases have been widely employed in formulating drug products, for example as emulsifiers, solubilizers, absorption enhancers, drug carriers in oral, periodontal, and vaginal delivery, and colloidal carrier systems [1]. GMO (or mono-olein) is a polar lipid composed of the monoglycerides of mainly oleic acid and other fatty acids such as linoleic, stearic, and palmitic acids. Based on the phase diagram described elsewhere [2], upon contact with water it swells to form different types of lyotropic liquid crystalline phases such as cubic (C), lamellar (L_α), reversed micellar (L_2), and reversed hexagonal phases (H_{II}), depending on the water content, temperature, and purity of the monoglyceride. Among the liquid crystalline phases, the cubic (25–35 w/w% water content) and lamellar (~5–20 w/w% water content) phases can offer a number of advantages for oral mucosal delivery of drugs, especially peptide and protein drugs because of their intrinsic properties. Some of those properties include: (a) the ability to incorporate various sizes of both

Copyright © 2003 Marcel Dekker, Inc.

hydrophilic and lipophilic drugs, (b) the mucoadhesive property, (c) the biocompatibility of GMO, and (d) the protective action of the cubic phase against enzymatic degradation of peptide drugs and against chemical instability of drugs [3–5]. Therefore, the drugs incorporated into the liquid crystalline phases of GMO can be delivered through the oral mucosa with therapeutic efficacy.

Drugs dispersed or dissolved in the liquid crystalline phases are delivered either locally or systemically. The work of Esposito et al. [6] has shown that the tetracycline-containing lamellar phase with low water content (<10% w/w) could be injected directly into the periodontal pocket. The free-flow lamellar phase was then transformed spontaneously to the gel by taking up the water surrounding the dose. Indeed, the highly structured cubic phase gel is formed from the semifluid lamellar phase by increasing either temperature or water content [7]. Since the rheological properties of the liquid crystalline phases of GMO are primarily governed by the ratio of water to GMO [8], one can design liquid crystalline formulations having various rheological states. Norling et al. [9], using GMO (monoglyceride) and sesame oil (triglyceride), formulated a metronidazole benzoate–containing periodontal delivery system. The sesame oil was added to the GMO to obtain an adequate consistency that allowed it to be administered with a syringe. Metronidazole benzoate suspended in a mixture of GMO and sesame oil was slowly released and this release process was controlled by hydration of the mixture, leading to the formation of liquid crystalline phases. This chapter will focus on liquid crystalline phases of GMO for use as systemic buccal delivery systems for peptide drugs.

II. LIQUID CRYSTALLINE ORAL MUCOSAL DELIVERY SYSTEMS FOR PEPTIDES

Buccal drug delivery has suffered from low bioavailability owing largely to the low mucosal membrane permeability, relatively small surface area available for absorption, and poor retention of delivery systems [10]. These problems can often be overcome by employing a mucoadhesive drug carrier. Cubic and lamellar liquid crystalline phases of GMO are considered promising buccal delivery systems for peptide and protein drugs since they are mucoadhesive and the cubic phase (fully swollen GMO) containing the equilibrium amount of water can protect peptide drugs from enzymatic degradation.

A. In Vitro Evaluation of Liquid Crystalline Phases of GMO

Lee and Kellaway have investigated the lamellar and cubic phases of GMO as buccal delivery carriers of a peptide, [D-Ala^2, D-Leu^5]enkephalin (DADLE, MW = 569.7) [11–13]. GMO itself and lamellar phases swell in the presence

Copyright © 2003 Marcel Dekker, Inc.

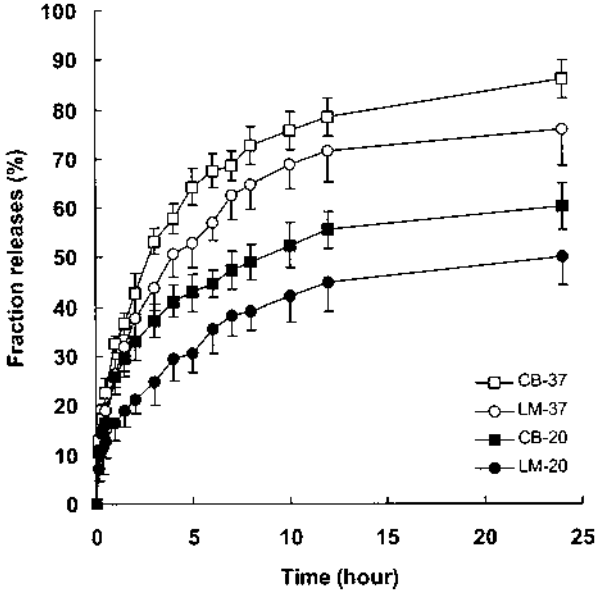


Figure 1 Cumulative amount of [D-Ala^2, D-Leu^5]enkephalin released from the liquid crystalline phases of glyceryl monooleate: CB, cubic phase; LM, lamellar phase; 37: measured at 37°C; 20: measured at 20°C. Mean ± SD, $n = 3$. (From Ref. [11].)

of water to form the cubic phase that contains the equilibrium amount of water. The cubic phase can coexist in equilibrium with an excess amount of water that does not modify the cubic phase structure. The swelling is mainly influenced by the initial water content and temperature. The water uptake increases with decreasing initial water content. The maximum water uptake at 20°C is higher than at 37°C. The cubic phases containing more than 35% w/w initial water are not swellable since they already contain the equilibrium amount of water. DADLE release occurs from the swelling liquid crystalline phases and the rate of release is governed by the initial water content and temperature. DADLE is released through hydrophilic channels located within the lamellar and cubic phases. Owing to greater amounts of initial water associated with the cubic phase, drug release is more rapid from the lamellar phase (Fig. 1). Temperature also has an appreciable effect on the drug release process. DADLE release increased at 37°C compared to 20°C owing to an increase in DADLE diffusivity within the liquid crystalline matrix at the higher temperature (Fig. 1). The linear relationship between the amount of drug released and square root of time suggested that drug release from the liquid crystalline phases is a diffusion-controlled process [11,14].

Copyright © 2003 Marcel Dekker, Inc.

B. Effect of Liquid Crystalline Phases of GMO on Buccal Permeation of Peptides

GMO can be liberated from the liquid crystalline matrix composed of GMO and water [12]. This released GMO permeates the porcine buccal mucosa. GMO permeation is significantly greater from the cubic phase than from the lamellar phase owing to the faster release of GMO from the cubic phase compared to the lamellar phase. Ex vivo DADLE permeation across the porcine buccal mucosa is higher from the liquid crystalline phases than from phosphate buffer solution (Fig. 2). This can be attributed to the rapidly released GMO from the liquid crystalline matrix acting as a permeation enhancer for DADLE by a cotransport mechanism of lipid and peptide. The greater in vitro release rates of DADLE and GMO from the cubic phase might also have led to the higher buccal permeation rate compared to the lamellar phase.

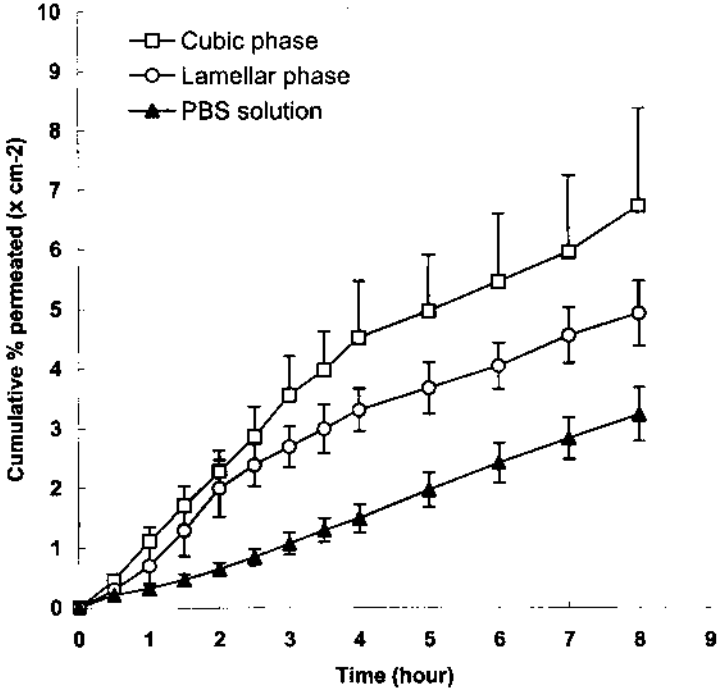


Figure 2 Ex vivo buccal permeation of [D-Ala^2, D-Leu^5]enkephalin from the liquid crystalline phases and aqueous phosphate buffered saline solution. Mean ± SD, $n = 5$. (From Ref. [12].)

Copyright © 2003 Marcel Dekker, Inc.

C. Enhancing Buccal Permeation of Peptides from the Cubic Phase of GMO

Permeation enhancement can be considered to further improve the buccal permeation rate of DADLE. Oleic acid (1.0% w/w) successfully increased the buccal mucosal membrane permeability of DADLE in the cubic phase with the aid of polyethylene glycol 200 (PEG 200) [13]. Oleic acid can be easily incorporated into the cubic phase, owing to its lipophilic nature, by solubilization within molten GMO. When oleic acid is used alone, the permeation-enhancing effect is poor. This is because most oleic acid is retained within the lipid domain of the cubic phase. The coadministration of PEG 200 with oleic acid resulted in increased oleic acid release from the cubic phase. PEG 200 was chosen as a coenhancer because it has the ability to solubilize oleic acid and does not cause a phase transition of the cubic phase when used at concentrations less than 10% w/w. The addition of oleic acid and PEG 200 did not change the in vitro release profile of DADLE from the cubic phase as it does not alter the essential structure of the cubic phase. Two mechanisms are suggested to explain the increased release rate of oleic acid by PEG 200. The partitioning of oleic acid between the lipophilic and hydrophilic domains of the cubic phase might be changed by PEG 200. Alternatively, PEG 200 may enhance the diffusion of water into the cubic phase matrix, thereby causing phase changes that influence oleic acid release.

PEG 200 plays a critical role in facilitating DADLE permeation rate across the buccal mucosa. The steady-state flux was significantly increased when oleic acid (1%) and PEG 200 (5–10%) were added to the cubic phase. On the other hand, 1% oleic acid alone and the combination of 1% oleic acid and 1% PEG 200 had no significant effect on the buccal permeation of DADLE although their mean fluxes slightly increased. The addition of PEG 200 alone with varying concentrations (1–10%) did not change the buccal permeation profile of DADLE. Therefore, it was evident that the appreciable enhancement of buccal permeation of DADLE from the cubic phase is due to the increased oleic acid solubility brought about by PEG 200. The oleic acid solubilized by PEG 200 can permeate the porcine buccal mucosa. The oleic acid permeation also increases with increasing PEG 200 concentration. The tissue accumulation of oleic acid also increases with increasing PEG 200 concentration, leading probably to greater lipid bilayer fluidization. Consequently, the coadministration of a lipophilic permeation enhancer and pharmaceutical solubilizer that increases the aqueous solubility of the lipophilic enhancer can offer optimization of the enhancing capability.

III. CONCLUSIONS

The liquid crystalline phases of GMO offer promising delivery vehicles for drug delivery to the oral mucosa. They offer a water-rich environment for the mucoad-

Copyright © 2003 Marcel Dekker, Inc.

hesive lamellar phase to swell to the cubic phase and subsequently to control the release of incorporated drugs. The water content plays an important role in oral mucosal liquid crystalline delivery systems, since it affects the mucoadhesive properties and the rheological characteristics of the liquid crystalline phases. In addition, the interaction of a drug with the liquid crystalline phases should be carefully examined as the amount and physicochemical properties of the drug may result in a phase change, leading to the modification of the drug release profile.

REFERENCES

1. A Ganem-Quintanar, D Quintanar-Guerrero, P Buri. Monoolein: a review of the pharmaceutical applications. Drug Dev Ind Pharm 26:809–820, 2000.
2. ST Hyde, B Ericsson, S Anderson, K Larsson. A cubic structure consisting of a lipid bilayer forming an infinite periodic minimum surface of the gyriod type in the glycerylmonooleate-water system. Z Kristallogr 168:213–219, 1984.
3. S Engström, H Ljusberg-Wahren, A Gustafsson. Bioadhesive properties of the monoolein-water system. Pharm Tech Eur 7:14–17, 1995.
4. B Ericsson, PO Eriksson, JE Lofroth, S Engström. Cubic phases as drug delivery systems for peptide drugs. ACS Symp Ser 469:251–265, 1991.
5. Y Sadhale, JC Shah. Glyceryl monooleate cubic phase gel as chemical stability enhancer of cefazolin and cefuroxime. Pharm Dev Technol 3:549–556, 1998.
6. E Esposito, V Carotta, A Scabbia, L Trombelli, P D'Antona, E Menegatti, C Nastruzzi. Comparative analysis of tetracycline-containing dental gels: poloxamer- and monoglyceride-based formulations. Int J Pharm 142:9–23, 1996.
7. S Engström, L Lindahl, R Wallin, J Engblom. A study of polar lipid drug carrier systems undergoing a thermoreversible lamellar-to-cubic phase transition. Int J Pharm 86:137–145, 1992.
8. J Lee, SA Young, IW Kellaway. Water quantitatively induces the mucoadhesion of liquid crystalline phases of glyceryl monooleate. J Pharm Pharmacol 53:629–636, 2001.
9. T Norling, P Lading, S Engstrom, K Larsson, N Krog, SS Nissen. Formulation of a drug delivery system based on a mixture of monoglycerides for use in the treatment of periodontal disease. J Clin Periodontal 19:687–692, 1992.
10. MJ Rathbone, BK Drummond, IG Tucker. The oral cavity as a site for systemic drug delivery. Adv Drug Del Rev 13:1–22, 1994.
11. J Lee, IW Kellaway. In vitro peptide release from liquid crystalline buccal delivery systems. Int J Pharm 195:29–33, 2000.
12. J Lee, IW Kellaway. Buccal permeation of [D-Ala^2, D-Leu^5]enkephalin from liquid crystalline phases of glyceryl monooleate. Int J Pharm 195:35–38, 2000.
13. J Lee, IW Kellaway. Combined effect of oleic acid and polyethylene glycol 200 on buccal permeation of [D-Ala^2, D-Leu^5]enkephalin from a cubic phase of glyceryl monooleate. Int J Pharm 204:137–144, 2000.
14. C-M Chang, R Bodmeier. Swelling of and drug release from monoglyceride-based drug delivery systems. J Pharm Sci 86:747–752, 1997.

Copyright © 2003 Marcel Dekker, Inc.

37

Microparticles as Delivery Systems for Local Delivery to the Oral Cavity

Rita Cortesi, Enea Menegatti, and Elisabetta Esposito
University of Ferrara, Ferrara, Italy

Claudio Nastruzzi
University of Perugia, Perugia, Italy

I. INTRODUCTION

As well as being a useful route for systemic drug delivery, a number of pathologies can be treated locally in the oral cavity, such as periodontal diseases [1], bacterial and fungal infections [2], dental stomatitis [3], and toothaches [4].

Various biodegradable polymers have been proposed as biomaterials for the production of oral mucosal drug delivery systems [5]. Biodegradable polymers have several advantages that make them useful as platforms for drug delivery systems. These include biocompatibility and the ability to control the release of incorporated drugs. Because of these advantages, various biodegradable oral mucosal dosage forms have been proposed and developed including tablets, films, ointments, and gels [6–8].

Examples of biodegradable polymers examined for potential oral mucosal drug delivery include poly (lactide-coglycolide) (PLG), polyanhydrides, poly(methyl methacrylate), and poly alkylcyanoacrylates [9]. Among them, PLG has been extensively studied. This class of polymers has been used for many years as an absorbable suture material with no known toxicity [9]. Drugs can be

Copyright © 2003 Marcel Dekker, Inc.

incorporated into this polymer either by a solvent evaporation technique [10] or by spray drying [11]. Owing to their potential application in oral mucosal drug delivery, polysaccharides and proteins have also been used to form different particulate systems such as polyacrylstarch microspheres, dextran nanospheres, and alginate particles. The advantage of using polysaccharides or proteins as delivery vehicles is related to their in vivo biodegradability [10].

II. MICROPARTICLES FOR ORAL MUCOSA DELIVERY

Biodegradable microparticles have been extensively employed as pharmaceutical formulations for many routes of drug delivery. However, to our knowledge very few papers have been published that propose the use of microparticles for oral mucosal drug delivery.

In general, microparticles offer a number of advantages with respect to other delivery systems since (a) their physicochemical characteristics remain unaltered for long periods allowing long-term storage, (b) depending on their composition, they can be administered by different routes (e.g., oral, oral mucosal, intramuscular, or subcutaneous), (c) they protect encapsulated drug from enzymatic- or pH-dependant degradation, (d) they are suitable for industrial production, and (d) microsphere-based formulations can be formulated to provide a constant drug concentration in the blood or to target drugs to specific cells or organs [12,13]. Microspheres can also be used to treat diseases that require a sustained concentration of the drug at a particular anatomical site, e.g., the periodontal pocket. In this regard, the relationship between anatomical site and microparticle size should be considered [14]. For instance, microspheres with diameters in the range of 20–120 μm can be utilized for oral, topical, subcutaneous, and periodontal pocket administration, since they are retained in the interstitial tissue and act as sustained-release depots. In contrast, smaller microparticles need to be prepared for application to other sites such as the eye, lung, and joints [14].

III. POTENTIAL APPLICATIONS

A. Delivery to the Periodontal Pocket

Recently, fibers, films, sponges, and microparticles have been proposed as effective methods to administer antibacterial agents for the treatment of dental pathological states affecting the gingival, subgingival, periodontal, and adjacent tissues, such as gingivitis and periodontitis [15]. Among these delivery systems, biodegradable microparticles appear the most advantageous since they can be easily administered and do not have to be removed after the treatment period. It has been shown that microparticles, after direct application to the periodontal

Copyright © 2003 Marcel Dekker, Inc.

pocket, can gradually release controlled amounts of drug for long periods (up to a month). The results suggest that this approach provides a constant and continuous level of drug and hence provides uniform therapy while minimizing associated side effects [10].

In this respect Esposito and colleagues [10] described the production, by different methods, of biodegradable microparticles for the administration of tetracycline in the oral cavity. Different polymers, such as poly(L-lactide) (L-PLA), poly(DL-lactide) (DL-PLA), and poly(DL-lactide-co-glycolide) 50:50 (DL-PLG), were investigated. The influence of polymer type and preparation procedure on microparticle characteristics (i.e., morphology and encapsulation yield) was studied. In addition, the authors studied the release characteristics of tetracycline from the microparticles. For microparticle production, different in-liquid drying processes were employed involving evaporation of a volatile solvent from (a) oil-in-water emulsion (o/w method) (Fig. 1A), (b) oil-in-oil system (o/o method) (Fig. 1B), and (c) water-in-oil-in-water double emulsion (w/o/w method) (Fig. 1C). Microparticles prepared by the o/w method showed a smooth surface, no aggregation phenomena, and good spherical geometry (Fig. 2A). However, this

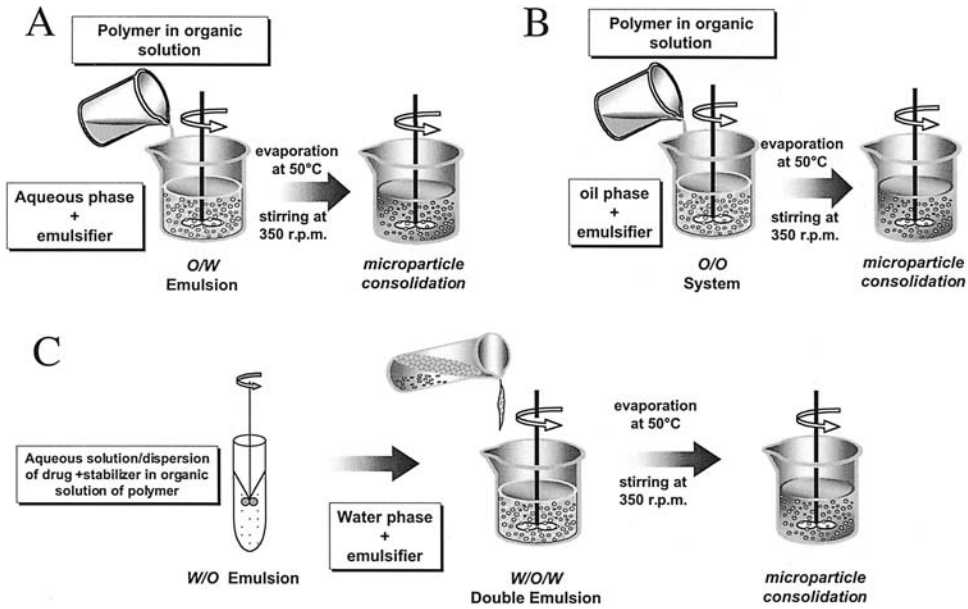


Figure 1 Schematic representation of microparticle production by liquid drying processes: (A) o/w emulsion method, (B) o/o system method, (C) w/o/w multiple emulsion method.

Copyright © 2003 Marcel Dekker, Inc.

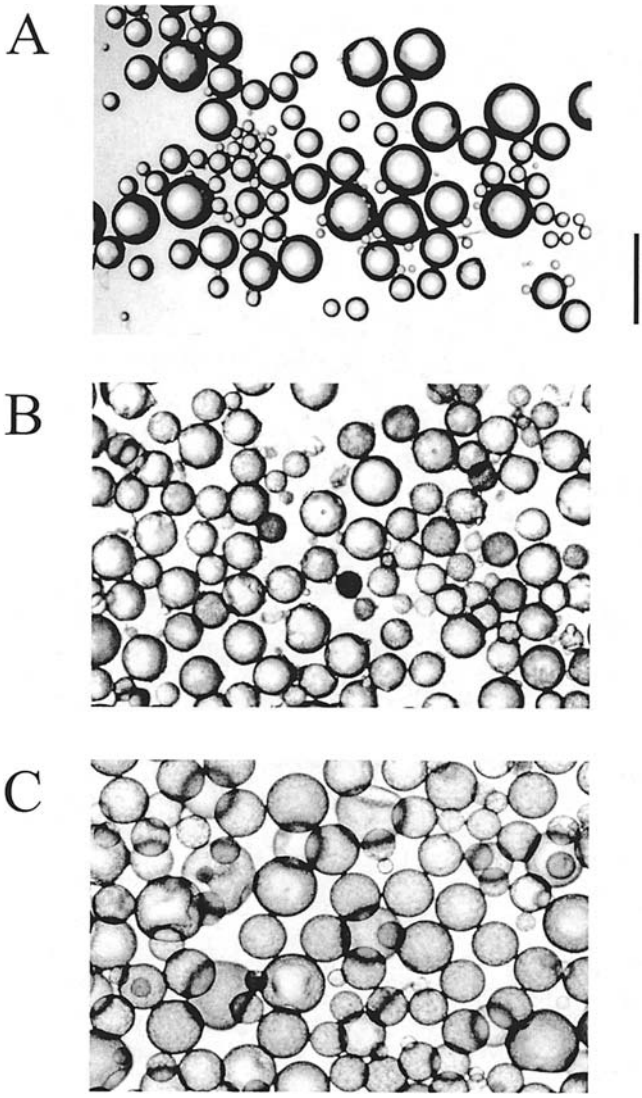


Figure 2 Optical photomicrographs of tetracycline containing PLG microparticles obtained by o/w (A), o/o (B), and w/o/w (C) methods. The bar corresponds to 19, 27, and 56 μm in panel A, B, and C, respectively.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Effect of Preparation Method on Tetracycline Incorporation Efficacy in Microparticles

Method (stabilizer)	Mean diameter (μm)	Incorporation efficacy (%)[a]		Notes
		TcHCl	TcB	
DL-PLG				
o/w	50.68	1	2.9	No aggregation
o/o	58.81			Significant aggregation, irregular shape
w/o/w (gelatin)	106.94	15	17	No aggregation, smooth, spherical
w/o/w (pectin)	120.22	10	<1	No aggregation, irregular shape
w/o/w (pemulen)	115.7	<1	<1	No aggregation, irregular shape
w/o/w (gelatin, NaCl)	111.92	26.62	n.d.	No aggregation, smooth, spherical
L-PLA				
w/o/w (gelatin, NaCl)	138.40	31.57	n.d.	No aggregation, smooth, spherical
DL-PLA				
w/o/w (gelatin, NaCl)	130.00	30.02	n.d.	No aggregation, smooth, spherical

[a] Percentage (w/w) of encapsulated drug with respect to the total amount used.
TcHCl = tetracycline hydrochloride; TcB = tetracycline free base; n.d. = not determined.

method gave a very poor incorporation efficacy of tetracycline hydrochloride (see Table 1). The scarce encapsulation was attributed to drug migration from the internal organic phase into the aqueous continuous phase during the in-liquid drying process. The second approach, the o/o method, was used to theoretically enhance the trapping efficiencies of hydrophillic compounds [16]. The aqueous continuous phase was replaced with light mineral oil, with the aim of preventing the partition or diffusion of the drug into the outer continuous phase. Microparticles produced by this method showed irregular shape, significant agglomeration, and the presence of tetracycline crystals on their surface (Fig. 2B). Finally, the

Copyright © 2003 Marcel Dekker, Inc.

w/o/w method enabled the investigators to obtain microparticles that were characterized by good morphology and encapsulation efficiency (Table 1, Fig. 2C). Using this last method of preparation, DL-PLA and L-PLA microparticles were also produced and physically characterized. The incorporation efficacy of tetracycline was enhanced by employing a concentrated NaCl solution (5% w/v) as the continuous phase [17] (Table 1). The morphology of DL-PLG, DL-PLA, and L-PLA microparticles is shown in Figure 3. In particular, DL-PLG microparticles (Fig. 3A) are characterized by a smooth surface with only few pores and a microcapsular structure, DL-PLA particles (Fig. 3B) are double-walled microcapsular systems and L-PLA particles are matrix-type microspheres showing high porosity (Fig. 3C).

The in vitro tetracycline release profile from microparticles was shown to be a function of the polymer matrix [10]. Esposito et al. [10] showed that drug release from DL-PLG particles was characterized by two almost linear portions with different slopes. In the case of DL-PLA, the initial phase of tetracycline release was characterized by a burst, while the second phase was almost superimposable on that of DL-PLG. Finally, tetracycline release from L-PLA microparticles was slower than that of the other polymers. This slow release was related to the high molecular weight (171,000). However, tetracycline was released in a controlled manner over about 1 month from all the above-described microparticles, suggesting their potential use in periodontal therapy.

B. Delivery of Recombinant Proteins

PLG microparticles have also been used as carriers for recombinant human bone morphogenic protein-2-driven recombinant regeneration [18]. In particular, these microparticles were used to support the recombinant protein and then positioned in transgingival tooth of dogs. Microparticles were produced by spray drying as described by Bodmeier and Chen [19]. After 8 weeks sacrificed animals showed a substantial bone regeneration indicating the effectiveness and quality of this carrier.

C. Delivery of Antigens

Biodegradable and bioadhesive starch microparticles (produced by Pharmacia, Hillerod, Dk) have also been used to deliver antigen and immunoglobulin A–enhancing cytokines to the oral mucosa [20]. The approach involved topical administration to the sublingual epithelium of the oral cavity of antigen in starch microparticles. Animals were subjected to three immunization cycles and sequential samples were assayed by radioimmunoassay for salivary IgA and antibodies after secondary and tertiary immunization. Salivary IgA responses were highest in alpha-lysophosphatidylcholine (penetration enhancer)–treated degradable

Copyright © 2003 Marcel Dekker, Inc.

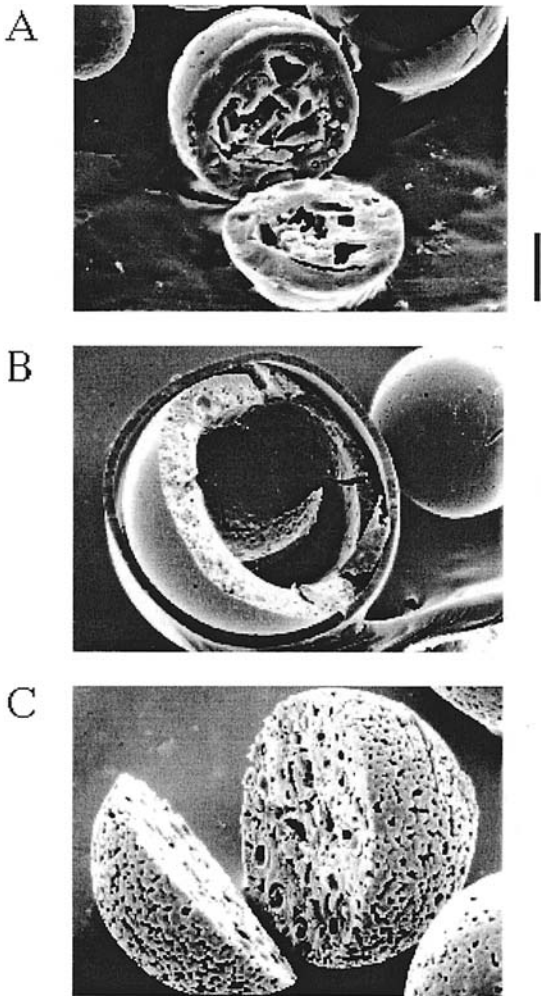


Figure 3 Scanning electron micrographs of DL-PLG (A), DL-PLA (B), and L-PLA (C) microparticles showing their external and internal morphology. The bar corresponds to 25, 34, and 40 μm in panels A, B, and C, respectively.

Copyright © 2003 Marcel Dekker, Inc.

starch microparticle groups at 71 days postsecondary immunization and continued up to 88 days posttertiary immunization. The results obtained by Montgomery and Rafferty [20] indicated that bioadhesive degradable starch microparticles can be used as a vehicle to deliver antigen and cytokine signals to the oral cavity. Moreover starch microparticles, when delivered in combination with a penetration enhancer, can potentiate long-term salivary IgA responses.

IV. CONCLUSIONS

Further in vivo studies will be necessary to better evaluate the suitability of microparticulate systems intended for local delivery of bioactive materials to sites in the oral cavity. Nevertheless, the main conclusion of this brief chapter is that the selection of appropriate preparation method and polymer type allows the production of biodegradable microparticles that can provide sustained delivery of a variety of drugs to various sites in the oral cavity.

REFERENCES

1. AEM Collins, PB Deasy, DJ MacCarthy, DB Shanley. Evaluation of a controlled release compact containing tetracycline hydrochloride bonded to tooth for the treatment of periodontal disease. Int J Pharm 51:103–114, 1989.
2. L Samaranayake, M Ferguson. Delivery of antifungal agents to the oral cavity. Adv Drug Del Rev 13:161–179, 1999.
3. T Nagai. Adhesive topical drug delivery system. J Control Rel 2:121–134, 1985.
4. M Ishida, N Nambu, T Nagai. Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose and carbopol. Chem Pharm Bull 30:980–984, 1982.
5. KK Peh, CF Wong. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. J Pharm Pharmaceut Sci 2:53–61, 1999.
6. JH Guo. Bioadhesive polymer buccal patches for buprenorphine controlled delivery: formulation, in vitro adhesion and release properties. Drug Dev Ind Pharm 20:2809–2821, 1994.
7. Y Kohda, H Kobayashi, Y Baba, H Yuasa, T Ozeki, Y Kanaya, E Sagara. Controlled release of lidocaine from buccal mucosa-adhesive films with solid dispersion. Int J Pharm 158:147–155, 1997.
8. JM Schor, SS Davis, A Nigalaye, S Bolton. Sudarin transmucosal tablets. Drug Dev Ind Pharm 9:1359–1377, 1983.
9. H Chen, R Langer. Oral particulate delivery: status and future trends. Adv Drug Del Rev 34:339–350, 1998.
10. E Esposito, R Cortesi, F Cervellati, E Menegatti, C Nastruzzi. Biodegradable microparticles for sustained delivery of tetracycline to the periodontal pocket: formulatory and drug release studies. J Microencap 14:175–187, 1997.

Copyright © 2003 Marcel Dekker, Inc.

11. JP Benoit, H Marchais, H Rolland, VV Velde. Biodegradable microspheres: advances in production technology. In: S Benita, ed. Microencapsulation: Methods and Industrial Applications. New York: Marcel Dekker, 1996, pp. 35–72.
12. DT O'Hagan. Microparticles and polymers for the mucosal delivery of vaccines. Adv Drug Del Rev 34:305–320, 1998.
13. AM Hillery. Microparticulate delivery systems: potential drug/vaccine carriers via mucosal routes. Pharmaceutical Science and Technology Today 1:69–75, 1998.
14. R Arshady. Microspheres, Microcapsules and Liposomes. London: Citus Book, 1999.
15. NJ Medlicott, MJ Rathbone, IG Tucker, DX Holborow. Delivery systems for the administration of drugs to the periodontal pocket. Adv Drug Del Rev 13:181–203, 1994.
16. R Wada, SH Hyon, Y Ikada. Lactic acid oligomer microspheres containing hydrophilic drugs. J Pharm Sci 79:919–924, 1990.
17. V Joly, GG Encina, MS Cohen, C Thies. Effect of salts on formation of lactide-glycolide microparticles in aqueous media. Proc Int Symp Control Rel Bioact Mater 21:282–283, 1994.
18. TJ Sigurdsson, L Nygaard, DN Tatakis, E Fu, TJ Turek, L Jin, JM Wozney, UM Wikesjo. Periodontal repair in dogs: evaluation of rhBMP-2 carriers. Int J Periodont Restor Dent 16:524–537, 1996.
19. R Bodmeier, H Chen. Preparation of biodegradable poly(±)lactide microparticles using a spray-drying technique. J Pharm Pharmacol 40:754–757, 1988.
20. PC Montgomery, DE Rafferty. Induction of secretory and serum antibody responses following oral administration of antigen with bioadhesive degradable starch microparticles. Oral Microbiol Immunol 13:139–149, 1998.

Copyright © 2003 Marcel Dekker, Inc.

38

OraVescent: A Novel Technology for the Transmucosal Delivery of Drugs

S. Indiran Pather, Rajendra K. Khankari, and John M. Siebert
CIMA LABS INC., Brooklyn Park, Minnesota, U.S.A.

I. INTRODUCTION

The OraVescent® SL and BL drug delivery systems have been designed to promote drug absorption through the oral mucosa (sublingual and buccal delivery, respectively). This may enable more rapid absorption of drugs that have a long T_{max}. In other instances, this route of administration may be desirable to avoid the first-pass effect and so improve the bioavailability of the drug. Some drugs are not absorbed to a significant extent when administered orally and delivery through the oral cavity mucosa may represent a convenient method of administration. The formulation of drugs of this type into tablets for transmucosal absorption may permit the replacement of an injection with such a tablet. In some instances the pathological condition of the patient detracts from efficient absorption of a drug that would otherwise be well absorbed. An obvious example is the case where the patient is vomiting frequently. In addition, gastrointestinal transit may be so severely compromised during a migraine attack as to render efficient drug absorption unlikely. Under these circumstances, a transmucosal system may be advantageous. The technology is protected by a patent, as described in the technical section below, and additional patents are pending.

Copyright © 2003 Marcel Dekker, Inc.

II. HISTORICAL DEVELOPMENT

The effervescence reaction has been known and utilized in pharmaceutical dosage forms for a long time, a patent having been issued in 1872 [1]. Carbon dioxide is released as a result of the interaction of an acid with a carbonate or a bicarbonate salt. More recently, Eichman and Robinson explored the potential for CO_2 to promote the transport of a drug across a biological membrane [2]. The mechanisms by means of which CO_2 acts as an absorption promoter were summarized as follows:

1. A solvent drag effect
2. Opening of tight junctions
3. Increase in the hydrophobicity of the cell membrane, thus promoting the absorption of hydrophobic drugs

The research described above illustrates the principle that effervescence can enhance drug absorption. However, these authors did not set out to develop a practical system that could be utilized in drug delivery, nor was such a system described. The present authors sought to utilize this principle to develop practical dosage forms. Systems that utilize effervescence for delivery of drugs through the oral mucosa (buccal and sublingual delivery) will be described in this chapter. Additional effervescent drug delivery systems for administration via other routes are detailed in pending patents applications but will not be described here as they are outside the scope of this section of the book.

The absorption enhancement illustrated by Eichman and Robinson may be improved by several additional effects, such as the use of mucoadhesives or additional penetration enhancers, and, in particular, by pH effects.

III. DESCRIPTION OF THE TECHNOLOGY

From a consideration of the Henderson-Hasselbach equation, it is known that pH values lower than the pK_a of a weak base promote its ionization in aqueous solution. On the other hand, when the pH of the solution is above the pK_a, the ionization of the weak base is repressed and the nonionized form predominates. The ionized form of the drug is much more water soluble than the nonionized form, whereas the latter is usually much more permeable to biological tissues. Therefore, conventional wisdom directs that a pH lower than the pK_a of the drug be used when the solubility of the drug is limited.

Where absorption of the weakly basic drug into a biological system is slow or incomplete, a pH somewhat higher than the pK_a of the drug may be chosen. This ensures that a significant proportion of the dissolved drug is in the un-ionized form and hence is more readily absorbed.

Copyright © 2003 Marcel Dekker, Inc.

Standard texts dealing with physical pharmacy usually portray these as opposite requirements: a low pH to promote dissolution and a higher pH to aid absorption. Often, the pH that is chosen is a compromise between that which is desirable for optimizing the solubility of the drug and that which promotes absorption [3]. The compromise implies a decrease in one potential to facilitate the other.

A variable pH would give the best of both worlds. If we could have a system that develops a low pH initially, the solubility of the weak base would be enhanced. If the pH of this system could then be made to slowly rise, the ionized form of the drug in solution would slowly change to the un-ionized form and, hence, absorption would be promoted. It is important that the pH change occur slowly, so that the concentration of the un-ionized form does not exceed its limited water solubility. Absorption of the drug into the biological tissues effectively reduces its concentration in solution and further helps to prevent precipitation from solution.

When the effervescence reaction occurs, CO_2 is liberated [Eq. (1)]. If a buccal or sublingual tablet contains the effervescent couple, the CO_2 that is released will dissolve in the saliva. The saliva becomes more acidic owing to the formation of carbonic acid [Eq. (2)]. Later, owing to the loss of CO_2 from solution, the pH of the solution gradually rises. The liberated CO_2 is either absorbed by the mucosal tissues where it might promote drug absorption, or it is lost to the air space in the oral cavity.

The overall pH variation with approximately equimolar amounts of citric acid and sodium bicarbonate is from about 6 to about 8.4, i.e., a variation of about 1 pH unit in either direction from normal salivary pH. This reaction, therefore, conveniently produces a changing pH profile that can be exploited for drug delivery. The upper and lower limits of the pH values that are covered by this dynamic system can be modified by the use of additional pH-adjusting substances, while maintaining a pH range of more than 2 units. For example, the pH range can be changed from ~5.5 to ~7.5 for use with a drug that has a pK_a of 6.5.

$$NaHCO_3 + C_3H_5O(COOH)_3 + H_2O \rightarrow CO_2 + 2H_2O + Na^+ + C_3H_5O(COOH)_2COO^- \quad (1)$$

$$CO_2 + H_2O \rightarrow H_2CO_3 \quad (2)$$

IV. RESEARCH AND DEVELOPMENT

The hypothesis that effervescence and the resulting pH transition can be utilized to enhance the delivery of poorly soluble weak bases was tested in human subjects with fentanyl as the model drug.

Copyright © 2003 Marcel Dekker, Inc.

Fentanyl was selected for the present study because its pK_a is 7.3 and its un-ionized form is highly lipophilic and poorly water soluble. Absorption of fentanyl from the gastrointestinal tract is slow and the drug also undergoes gut wall, and extensive hepatic, metabolism. Only about one-third of a swallowed dose is absorbed. Fentanyl is thus an ideal drug to test the hypothesis outlined above because its physicochemical characteristics fit the model well and there is a reduced tendency for gastrointestinal absorption (from swallowed drug) to confuse the assessment of oral transmucosal absorption.

The study was conducted in Belfast, Northern Ireland and the protocol was approved by the Ethics Committee of Queen's University of Belfast. Twelve normal, healthy male volunteers aged 18–55 years participated in the study. Each subject's body weight was not more than 15% above or 15% below the ideal weight for his height and estimated frame, adapted from the 1983 Metropolitan Life Table. After an overnight fast, the subjects were given one of three dosing regimens according to a randomization schedule:

1. An OraVescent fentanyl buccal tablet
2. A tablet that was similar to (1) in size, shape, and drug content but contained lactose in place of the absorption-enhancing components
3. An Actiq® oral transmucosal delivery system, which is marketed by Anesta Corporation in the United States

Water was allowed ad lib except for the period from dosing to 4 h postdose. Subjects followed a menu and meal schedule as determined by the clinic with the first meal approximately 5 h after dosing.

Subjects taking treatments (1) and (2) were asked to place the tablet between the upper gum and the inside of the cheek, above a premolar tooth. The tablets were left in place for 10 min. If, at that time, a subject felt that a portion of the tablet remained undissolved, he was requested to gently massage the area of the outer cheek, corresponding to the tablet's placement, for a maximum of 5 min. A member of the clinic staff checked the subject's mouth at 15 min to see if any portion of the tablet remained. The residue, if any, was allowed to dissolve on its own without further manipulation.

Administration of treatment (3) was according to the directions on the package insert of the product. After removal from the wrapper, the candy-based delivery system was placed between the lower gum and cheek with the handle protruding from the subject's mouth. From time to time, the unit was moved to the other side of his mouth. Subjects were instructed to suck and not to chew the unit.

After dosing, blood samples were withdrawn at predetermined time points for 36 h. The blood samples were centrifuged and the separated serum was frozen until assayed by an LC/MS/MS method. The assay method was sufficiently sensitive to allow a limit of quantitation of 0.05 ng/mL.

Copyright © 2003 Marcel Dekker, Inc.

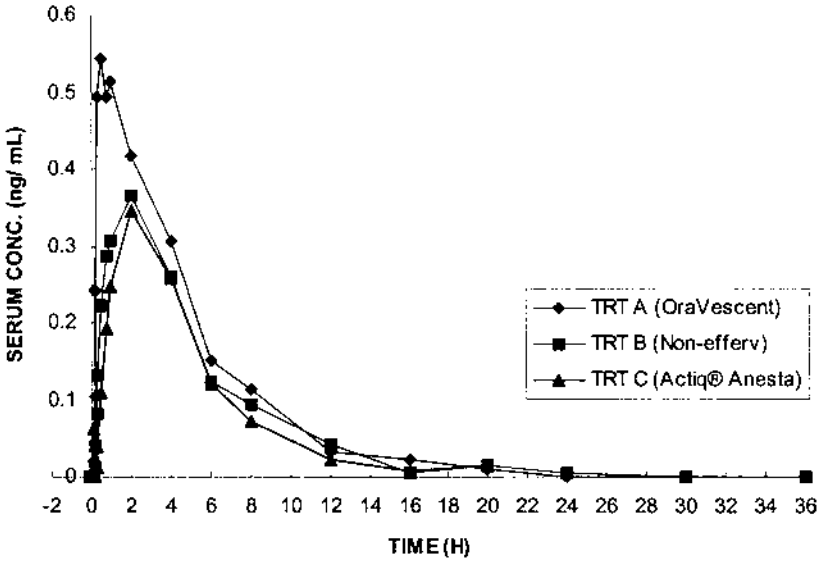


Figure 1 Fentanyl bioavailability after buccal administration.

The serum level versus time plots are shown in Figure 1 while the pertinent pharmacokinetic parameters are summarized in Table 1. The OraVescent enhanced delivery system displayed superior pharmacokinetics when compared to either the nonenhanced tablet (2) or the commercial dosage form (3). A comparison of the enhanced and nonenhanced formulations (1 versus 2) indicates that the enhanced delivery system functioned as intended; i.e., effervescence promoted absorption. The following comparisons can be made of fentanyl pharmacokinetics after OraVescent versus Actiq administration:

Table 1 Summary of Fentanyl Pharmacokinetics

	OraVescent buccal (1)	Nonenhanced buccal (2)	Actiq (3)
C_{max} (ng/mL)	0.6412 (±0.2804)	0.3986 (±0.0744)	0.4073 (±0.1537)
AUC (0-t) (ng/hr/mL)	2.656 (±0.6729)	2.041 (±0.8690)	1.809 (±0.9358)
Median T_{max} (h)	0.501	2	2

All values for OraVescent are significantly different compared to corresponding values for the nonenhanced tablet and Actiq.

Copyright © 2003 Marcel Dekker, Inc.

1. Fentanyl peak serum levels are higher (0.6 ng/mL compared to 0.4 ng/mL).
2. Systemic fentanyl bioavailability is more complete (the AUC is approximately 1.47 times as high).
3. Fentanyl is more rapidly absorbed (T_{max} is 0.5 h compared to 2 h).

In Figure 2, the serum levels obtained during the first 30 min are plotted on an expanded scale. These graphs clearly reveal the faster absorption of fentanyl from the OraVescent formulation during the initial stages. The rapid initial rise in fentanyl serum levels indicates that the delivery system has the potential to provide quicker onset of pain relief.

Fentanyl is an anesthetic agent that may be used for induction of anesthesia and, in combination with other anesthetic agents, in the postinduction phase [4]. It is also used for the treatment of moderate to severe chronic pain, such as that experienced by cancer patients. For this purpose, it is often administered as a transdermal drug delivery system [5]. This system provides continuous delivery of the medication for 72 hours and its efficacy and safety have been established [6]. An example of such a system is Duragesic® transdermal system (Jansen Pharmaceutica Products, L.P). Cancer patients often experience severe pain of short duration while on an otherwise adequate dose of fentanyl, or other long-acting formulation. For relief of this "breakthrough" pain, an additional low-dose, quick-acting medication is needed. Rapidity of onset of action of the supple-

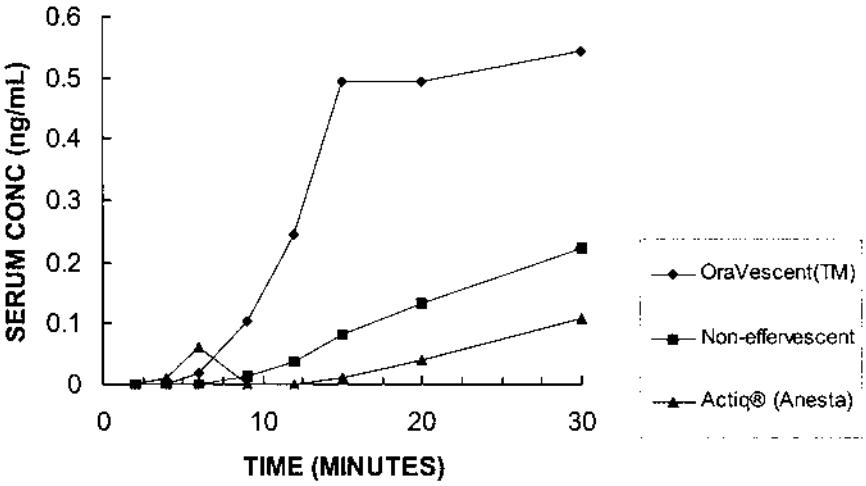


Figure 2 Early-phase fentanyl serum levels.

Copyright © 2003 Marcel Dekker, Inc.

mentary medication is essential. The OraVescent fentanyl drug delivery system (DDS) is designed to fulfill this requirement.

Comparing OraVescent fentanyl to the other two products, Table 1 shows that drug absorption was faster (t_{max} is shorter) and more complete (AUC is greater) and that the peak serum levels were higher. These differences are statistically significant ($p < 0.05$). Figure 2 clearly shows the much more rapid initial rise in serum fentanyl levels with the OraVescent DDS.

The results of this study show that the OraVescent DDS functioned as intended; i.e., the system promoted the absorption of a weak base. A rapid initial rise in serum levels and a faster and more complete absorption, relative to the commercial product, was observed. OraVescent fentanyl, therefore, has the potential for a quicker onset of action and may be useful for the relief of breakthrough cancer pain.

Additional studies were also conducted comparing the buccal and the sublingual routes for OraVescent fentanyl administration, and OraVescent fentanyl versus Actiq pharmacokinetics under simulated self-administration in which the subjects were only given written instructions. The rank order of the results was similar to those described above.

V. FUTURE DIRECTIONS

Other molecules that could potentially benefit from the OraVescent technology are being investigated at present.

REFERENCES

1. WT Cooper. Improvements in preparing or making up medicated and other effervescing mixtures. British patent 3160, 1872.
2. JD Eichman, JR Robinson. Mechanistic studies on effervescent-induced permeability enhancement. Pharm Res 15:925–930, 1998.
3. A Martin. Physical Pharmacy. 4th ed. Philadelphia: Lea & Febiger, 1993.
4. D Kietzmann, D Hahne, TA Crozier, W Weyland, P Groger, H Sonntag. Comparison of sufentanil-propofol-anesthesia with fentanyl-propofol in major abdominal surgery. Anaesthesist 45:1151–1157, 1996.
5. LY Yee, JR Lopez. Transdermal fentanyl. Ann Pharmacother 26:1393–1399, 1992.
6. MA Southam. Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy. Anticancer Drugs 6:29–34, 1995.

Copyright © 2003 Marcel Dekker, Inc.

39
Dermal and Transdermal Delivery

Jonathan Hadgraft
Medway Sciences, NRI, University of Greenwich, Chatham, England

I. DERMAL VERSUS TRANSDERMAL DRUG DELIVERY

There are many similarities, but also differences, in delivering medicinal agents for dermal as opposed to transdermal use. In the former, uptake into the systemic circulation is not required and is probably unwanted, whereas in the latter, it is a prerequisite. In transdermal applications the medicine will be delivered to intact, healthy skin. In contrast, in dermal applications often the barrier properties are impaired as the formulation is being used to treat a diseased state. This adds the complexity that high drug amounts will reach the underlying tissues during the first applications, but as the disease state is treated and the skin heals, drug permeation becomes more and more difficult and lower concentrations will be reached. This problem is particularly pronounced in the area of wound healing, as discussed elsewhere in this book. As our knowledge of the biochemical needs for treatment of disease advances, it should be possible to provide dermal formulations with programmed delivery that address at least some of these difficulties.

II. THE CHALLENGE

It is rare that the industry produces a new chemical entity specific for dermal or transdermal use and often, therefore, its inherent physicochemical properties are not ideally suited to uptake into and through the skin. This means that considerable effort has to be expended on the appropriate design of a formulation or a device to deliver enough of the medicine such that there is sufficient present at its site of action. The recent advances and development of biotechnology agents

Copyright © 2003 Marcel Dekker, Inc.

have increased this problem as these materials are usually large and have properties that are incompatible with easy transfer through the skin.

III. TRANSDERMAL DRUG DELIVERY

In the late seventies transdermal drug delivery was heralded as a methodology that could provide blood levels controlled by the device [1]. There was an expectation that it could therefore develop into a universal strategy for the administration of medicines. For a variety of reasons these hopes have not been fulfilled. However, this route for drug delivery remains attractive and offers many benefits.

A. Advantages

The skin offers several advantages as a route for drug delivery [2]. In most cases, although the skin itself controls drug input into the systemic circulation, drug delivery can be controlled predictably, and over a long period of time, from simple matrix-type transdermal patches.

The resultant drug levels are usually constant over the lifetime of the patch, and the peaks and troughs in plasma levels associated with conventional oral dosing are avoided.

Programmed delivery from conventional transdermal patches is not easy but the techniques that use active processes, such as an electric current, can deliver the active in a time-dependent manner [3]. This will be particularly important where the physiological need can change with time throughout the day. In the past there has been little recognition of the relative importance of this but advances in chronopharmacokinetics have highlighted advantages of this approach to rational therapy [4].

Another advantage of transdermal delivery is the ability to avoid first-pass metabolism and also to circumvent the hostile environment of the gastrointestinal tract. How much of a problem exists is very dependent on the properties of the medicinal agent, but it should be remembered that the skin is capable of metabolizing some permeants [5].

The deeper layers of the skin are metabolically more active than the stratum corneum. But even in this "dead" layer proteases are present that could degrade some of the topically applied biotech agents as they diffuse through the skin [6,7].

Finally, a further advantage of the transdermal route is that patient compliance and the acceptance of transdermal delivery appear to be excellent [8].

Copyright © 2003 Marcel Dekker, Inc.

B. Problems

Since the inception of transdermal drug delivery there has only been a very limited number of products launched onto the market. There are various reasons for this. The skin is a very effective barrier for the permeation of most xenobiotics. A typical drug that is incorporated into a dermal drug delivery system will exhibit a bioavailability of only a few percent [9]. Therefore, the active has to have a very high potency. Considering that topical drug delivery systems typically are applied at a few mg/cm^2 and that they contain only a few percent of the active, very little drug actually arrives at the site of action. For transdermal delivery, as a rule of thumb, the maximum daily dose that can permeate the skin is of the order of a few milligrams. This underscores the need for high-potency drugs.

The required high potency can also mean that the drug has a high potential to be toxic to the skin (e.g., irritancy or a sensitization).

If the barrier function of the skin is compromised in any way, some of the matrix-type delivery devices can deliver more of the active than necessary and the transdermal equivalent of "dose dumping" can occur.

In all transdermal systems it is recommended that when a patch needs changing it is applied to a new site. Elevated drug levels can be produced if a new patch is placed immediately at the old site and there will be the possibility of enhanced skin toxicity. The skin is a dynamic organ with its surface sloughing off continuously as new cells are forced up from the basal layer. The dynamics may be perturbed under the occlusive nature of a transdermal patch and the hydration levels of the stratum corneum raised. The barrier function of the skin should be allowed to return to normal before a patch is reapplied to the site.

Finally, the manufacturing costs of the patches or devices have to be taken into consideration. This is not a simple evaluation, as it will include considerations such as the relative cost of active, quality-of-life assessments, and whether it will reduce the amount of time a patient is hospitalized [10].

C. The Skin as a Barrier

The first of the two major problems associated with dermal delivery is the excellent barrier property of the skin. This resides in the outermost layer, the stratum corneum. This unique membrane is only some 20 μm thick but has evolved to provide a layer that prevents us from losing excessive amounts of water and limits the ingress of chemicals with which we come into contact. The precise mechanisms by which drugs permeate the stratum corneum are still under debate but there is substantial evidence that the route of permeation is a tortuous one following the intercellular channels. The diffusional pathlength is between 300

Copyright © 2003 Marcel Dekker, Inc.

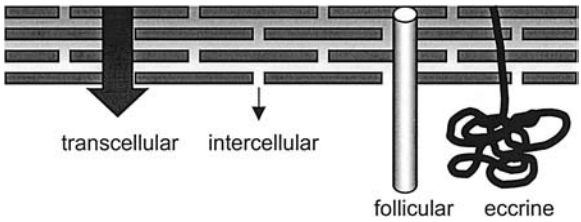


Figure 1 A schematic of the skin showing the different possible routes of penetration.

and 500 μm rather than the 20 μm suggested by the thickness of the stratum corneum [11]. However, the tortuosity alone cannot account for the impermeability of the skin. The intercellular channels contain a complex milieu of lipids that are structured into ordered bilayer arrays [12]. It is the combination of the nature of these and the tortuous route that is responsible. A diffusing drug has to cross, sequentially, repeated bilayers and therefore encounters a series of lipophilic and hydrophilic domains. A diagrammatic representation of the various routes of penetration is shown in Figure 1.

The physicochemical properties of the permeant are therefore crucial in dictating the overall rate of delivery [13]. A molecule that is hydrophilic in nature will be held back by the lipophilic acyl chains of the lipids, and conversely, a lipophilic permeant will not penetrate well through the hydrophilic head-group regions of the lipids. Furthermore, the lipids appear to pack together very effectively, creating regions in the alkyl chains close to the head groups that have a high microviscosity. This creates multiple layers in which diffusion is comparatively slow.

D. Factors Affecting Skin Permeation

Given the excellent barrier property of the skin, it is not surprising that few compounds permeate the skin well. Those that do tend to be relatively small and have balanced lipid water partition behavior and good solubility in both oils and water. For this reason compounds such as nitroglycerin and nicotine permeate the skin well [14]. Even so, the total daily dose that can be delivered over a reasonable surface area is only of the order of milligrams. As will be seen later in this chapter, the physicochemical properties that dominate the success of the technique for passive delivery are predominantly the partition coefficient and solubility. Where current is used to drive the drug through the skin, charge and size effects are important. It is possible to perturb these effects. If there are regions of the permeant that allow it to adsorb onto the "pore" walls through which it

Copyright © 2003 Marcel Dekker, Inc.

is moving, the surface potential of the pore can be altered, which in turn can affect the efficiency of delivery [15].

E. Permeation Enhancement

1. Chemical Approaches

The impermeability of the skin has led to the development of a number of enhancement strategies. These can be broadly divided into chemical and physical approaches.

Chemical methods can be further subdivided. There are methods that produce the active at a very high thermodynamic activity [16]. This can involve the loss of a solvent, which may occur as a result of its evaporation or its diffusion into the skin. Alternatively, the polymer matrix may take up water from the skin, which can alter the polymer's solubility properties such that the permeant becomes "supersaturated." The active is often present in the polymer matrix at as high a loading concentration as possible and is therefore close to saturation. This can cause stability issues, and permeation rates from devices have been observed to change with time, especially if the expiration date has been exceeded [17].

The second "chemical" enhancement mechanism is to use solvents that permeate into the skin and act essentially as a carrier for the active [18]. In some reservoir-type patches there will be a solvent in the reservoir, such as ethanol, that can codiffuse with the active facilitating its passage through the stratum corneum.

The third mechanism is one in which a component of the formulation permeates into the intercellular lipids where it intercalates and disrupts their structure [18]. This creates a region where diffusion is faster and permeation through the stratum corneum is improved. The molecular structure of this type of enhancer tends to possess a long alkyl chain and a polar head group; i.e., it is surfactant-like. It is possible that this type of molecule can also have irritant properties and it is obvious that materials have to be selected that affect the barrier function in a reversible manner. They must not disrupt the membranes of the viable cells in the deeper layers of the skin where they could elicit adverse effects.

It is possible that the enhancement that occurs with transdermal drug delivery systems is a result of more than one of the above factors. For example, if a combination of enhancers is used, one that acts as a good solvent and one that disrupts the lipid structure, a multiplicative effect can be found. There is also the possibility that the solvents may actually abstract some of the skin lipids making precise interpretation of the overall mechanism even more complex [19].

Different chemical entities that have been used to enhance transdermal delivery are shown in Table 1.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Typical Enhancers Used in Transdermal Delivery

Active	Patch	Enhancer
Fentanyl	Duragesic	Ethanol
Nitroglycerin	Nitrodisc	Isopropyl palmitate
	Nitrol	Lauryl alcohol
		Isopropyl palmitate
Estradiol	Estraderm	Ethanol
	Climara	Isopropyl myristate
		Glyceryl mono-laurate
	Trial Sat	Oleic acid
		Propylene glycol
	Vivelle	Oleic acid
	Menorest	1,3-Butylene glycol
		Lecithin
		Dipropylene glycol
		Propylene glycol
Testosterone	Androderm	Glyceryl monooleate
		Methyl laurate
		Ethanol

2. Iontophoresis

With the development of biotech drugs and the need to deliver peptides and oligonucleotides (or their analogs) it was clear that the physicochemical properties of this type of compound precluded transdermal delivery using conventional enhancer approaches. Most peptides are charged and therefore there was a renaissance in iontophoresis [20]. This technique has been known for many years with some of the pioneering studies conducted as far back as the nineteenth century. Delivery of charged entities adds a degree of complexity to transdermal delivery. The process is dominated by the physicochemical properties of the active, and its charge state as it moves through the strata of the skin has to be considered. The pH of the stratum corneum varies from the surface (pH 4–5) to physiological pH at the viable epidermis interface. If the pK_a of the permeant is between these values, charge reversal can occur. The electrode driving the active into the skin becomes attractive to it and therefore it will not be driven into the deeper tissues where it is required for systemic absorption. Although predominantly considered for the delivery of charged entities, iontophoresis can also facilitate the absorption of uncharged hydrophilic species by the process of electro-osmosis [21].

One of the advantages of using active delivery methods is that it is possible

Copyright © 2003 Marcel Dekker, Inc.

to combine delivery with analysis of the blood levels. With the advances in nanotechnology and analytical procedures using appropriate biosensors, either the permeant can be measured or a biochemical marker for its activity [22]. As an example, it is possible to use reverse iontophoresis to measure glucose levels in the blood. However, it must be remembered that it is very difficult to deliver insulin transdermally [23].

3. Other Physical Approaches

The developments of iontophoresis also promoted research into other physical methods of delivering transdermally; these include electroporation and ultrasound (or sonophoresis). The barrier function of the skin can also be physically breached by "shooting" particles through it using high velocities or by ablating the stratum corneum by precisely controlled laser technology. Microneedles can also be developed to pierce the skin to allow delivery to carefully controlled depths.

IV. EVALUATING DELIVERY THROUGH THE SKIN

In the development of transdermal drug delivery systems it is important to determine the effectiveness of delivery of the drug to the site of action, usually the systemic circulation. Before in vivo work can be conducted it is important to have some idea of expected plasma levels. To a degree this can be achieved using in vitro skin models and using the steady-state flux data from these to estimate the drug input into the body. If this is equated to the clearance kinetics, reasonable predictions can be made about the expected steady-state plasma levels [24]. Ideally, human skin is used for these experiments as animal skin rarely gives accurate estimations. In general, animal skin is more permeable than human skin. In vitro experiments can be misleading if the skin metabolizes the active during its permeation to the blood supply. Guidelines for setting up methodologies for skin permeation studies are readily available in the literature [25]. It is less clear how to establish reproducible techniques for assessing transdermal delivery when invasive procedures such as laser ablation or needles are involved.

V. REGULATORY ISSUES

The role of any regulatory authority is to ensure a safe and effective medicine. In the case of transdermal drug delivery a number of issues need to be considered. They have to take into account the drug, the excipients, and the device. The active has to be delivered at an adequate rate through the skin and it should have no adverse effects on the skin. It is surprising how many chemical entities have

Copyright © 2003 Marcel Dekker, Inc.

some degree of skin toxicity, irritancy, or allergenicity. This can be exacerbated by solvents in the delivery system such as those present to solubilize the medicine or to enhance its passage through the skin. Enhancers have already been discussed above, but it is essential to choose agents that are toxicologically safe and do not alter the barrier function of the skin in an irreversible way. It is possible for solvents to leach components of the patch, such as plasticizers present in the polymers/adhesives. The safety of these issues needs to be tested carefully. For active delivery systems it is important to ensure that the devices are capable of delivering the drug in a reproducible way to skin sites that may vary considerably in permeability characteristics.

Stability is also an area of interest. Often transdermal patches have high drug loads to minimize their surface area. The active is often close to saturation; care needs to be taken that crystallization on storage does not influence the effectiveness of the medication. In the case of iontophoresis, the drug flux will be proportional to the current. Tests will need to show that constant current is provided over a range of conditions and after storage of the devices.

VI. THE FUTURE

The development of medicines is becoming increasingly costly. The active materials are becoming far more active and selective and need to be delivered in a carefully controlled manner. This is possible with the types of technology described later in this book. The relative costs of using a complex sophisticated delivery system will become less of a problem in the future. It is possible that some of the skin toxicity problems will be conquered using biotechnology agents that can suppress the toxic responses. These biotechnology agents will need to be delivered carefully and concurrently with the medicine. There are no reasons why this should not be a successful means of accessing a far wider range of medicines that otherwise could not be delivered using this attractive route of administration. Noninvasive monitoring of drug levels or of other biological markers will become routine and it should be possible to program drug delivery accurately and only when required. The vision of the seventies, that transdermal delivery could be universally realizable, is a possibility but requires technological advances. The following chapters show the different ways in which transdermal delivery could easily be advanced well into the century.

REFERENCES

1. JE Shaw. Controlled topical delivery of drugs for systemic action. Drug Metab Rev 8:223–233, 1978.

Copyright © 2003 Marcel Dekker, Inc.

2. J Hadgraft. Advances in transdermal drug delivery. Practitioner 240:656–658, 1996.
3. RH Guy. Iontophoresis—recent developments. J Pharm Pharmacol 50:371–374, 1998.
4. JM Gries, N Benowitz, D Verotta. Importance of chronopharmacokinetics in design and evaluation of transdermal drug delivery systems. J Pharmacol Exp Ther 285: 457–463, 1998.
5. I Steinstrasser, HP Merkle. Dermal metabolism of topically applied drugs: pathways and models reconsidered. Pharm Acta Helv 70:3–24, 1995.
6. M Brattsand, T Egelrud. Purification, molecular cloning, and expression of a human stratum corneum trypsin-like serine protease with possible function in desquamation. J Biol Chem 274:30033–30040, 1999.
7. B Sondell, LE Thornell, T Egelrud. Evidence that stratum-corneum chymotryptic enzyme is transported to the stratum-corneum extracellular-space via lamellar bodies. J Invest Dermatol 104:819–823, 1995.
8. RK Simpson, EA Edmondson, CF Constant, C Collier. Transdermal fentanyl as treatment for chronic low back pain. J Pain Symp Manage 14:218–224, 1997.
9. RJ Feldmann, HI Maibach. Regional variation in percutaneous penetration of ^{14}C cortisol in man. J Invest Dermatol 48:181–183, 1967.
10. DM Neighbors, TJ Bell, J Wilson, SL Dodd. Economic evaluation of the fentanyl transdermal system for the treatment of chronic moderate to severe pain. J Pain Symptom Manage 21:129–143, 2001.
11. RO Potts, ML Francoeur. The influence of stratum corneum morphology on water permeability. J Invest Dermatol 96:495–499, 1991.
12. PA Cornwell, BW Barry, CP Stoddart, JA Bouwstra. Wide-angle X-ray diffraction of human stratum corneum: effects of hydration and terpene enhancer treatment. J Pharm Pharmacol 46:938–950, 1994.
13. G Flynn. Physicochemical determinants of skin absorption. In: TR Gerrity, CJ Henry, eds. Principles of Route-to-Route Extrapolation for Risk Assessment. New York: Elsevier, 1990, pp. 93–127.
14. J Hadgraft. Pharmaceutical aspects of transdermal nitroglycerin. Int J Pharm 135: 1–11, 1996.
15. MB Delgado-Charro, AM Rodriguez-Bayon, RH Guy. Iontophoresis of nafarelin: effects of current density and concentration on electrotransport in vitro. J Control Rel 35:35–40, 1995.
16. MA Pellett, MS Roberts, J Hadgraft. Supersaturated solutions evaluated with an in vitro stratum corneum tape stripping technique. Int J Pharm 151:91–98, 1997.
17. KR Brain, J Hadgraft, VJ James, VP Shah. In vitro assessment of skin permeation from a transdermal system for the delivery of oestradiol. Int J Pharm 89:R13–R16, 1993.
18. J Hadgraft. Passive enhancement strategies in topical and transdermal drug delivery. Int J Pharm 184:1–6, 1999.
19. D Bommannan, RO Potts, RH Guy. Examination of the effect of ethanol on human stratum corneum in vivo using infrared spectroscopy. J Control Rel 16:299–304, 1991.
20. J Hirvonen, YN Kalia, RH Guy. Transdermal delivery of peptides by iontophoresis. Nature Biotechnol 14:1710–1713, 1996.

Copyright © 2003 Marcel Dekker, Inc.

21. RH Guy, YN Kalia, MB Delgado-Charro, V Merino, A Lopez, D Marro. Iontophoresis: electrorepulsion and electroosmosis. J Control Rel 64:129–132, 2000.
22. V Merino, A Lopez, D Hochstrasser, RH Guy, Noninvasive sampling of phenylalanine by reverse iontophoresis. J Control Rel 61:65–69, 1999.
23. SK Garg, RO Potts, NR Ackerman, SJ Fermi, JA Tamada, HP Chase. Correlation at fingerstick blood glucose measurements with GlucoWatch biographer glucose results in young subjects with type 1 diabetes. Diabetes Care 22:1708–1714, 1999.
24. VM Knepp, J Hadgraft, RH Guy. Transdermal drug delivery: problems and possibilities. Crit Rev Ther Drug Carr Syst 4:13–37, 1987.
25. JP Skelly, VP Shah, HI Maibach, RH Guy, RC Wester, GA Flynn, A Yacobi. FDA and AAPS report of the workshop on principles and practices of in vitro percutaneous penetration studies: relevance to bioavailability and bioequivalence. Pharm Res 4:265–267, 1987.

Copyright © 2003 Marcel Dekker, Inc.

40
D-TRANS Technology

Rama Padmanabhan, Robert M. Gale, J. Bradley Phipps
William W. van Osdol, and Wendy Young
ALZA Corporation, Mountain View, California, U.S.A.

I. INTRODUCTION

Transdermal drug delivery is the delivery of drugs through intact skin at controlled rates selected to maximize therapeutic efficacy. D-TRANS® transdermal therapeutic systems (developed by ALZA Corporation, Mountain View, CA) are designed to provide improved bioavailability and increased drug absorption, improved comfort and ease of application, reduced dosing frequency, and controlled delivery.

Although the skin has been used as a route of drug delivery throughout history (e.g., plasters and poultices), it is only within the last few decades that scientists have gained an increased understanding of the skin and its barrier properties. This greater knowledge has led to the development of more reliable and efficacious means of safely delivering therapeutic agents through the skin.

Topical formulations of drugs are the simplest types of transdermal drug delivery systems used today. These systems utilize a liquid, gel, or cream as a vehicle for direct application to the skin. Drug from these systems penetrates into the skin to produce a pharmacological response, usually for only a short period of time. D-TRANS® transdermal therapeutic systems improve upon this concept by providing a more prolonged delivery and a more reliable means of administering drug through the skin for systemic applications.

Copyright © 2003 Marcel Dekker, Inc.

II. D-TRANS TRANSDERMAL THERAPEUTIC SYSTEMS

A. Description

D-TRANS® transdermal systems provide rate-controlled administration of drugs through a patch resembling a small adhesive bandage that is placed on the surface of intact skin. Their functionality is analogous to that of a continuous intravenous or subcutaneous infusion. Their design varies according to drug delivery requirements, but most systems consist of a series of thin, flexible membranes comprising a backing, a drug reservoir, a rate-controlling polymer membrane, and an adhesive. The rate-controlling membrane in these systems separates the drug reservoir from the skin and controls the drug release into the skin.

B. Rationale for Development of D-Trans Technology

Transdermal therapeutic systems were developed to address therapeutic and marketing needs not met by other drug delivery technologies, as summarized in Table 1. The systems potentially provide advantages such as enhanced safety, efficacy, reliability, and acceptability of drug treatment [1,2].

1. Theory and Mechanisms

The stratum corneum, the uppermost epidermal layer, is composed of terminally differentiated keratinocytes (corneocytes) in a matrix of lipid lamellae (the so-called "bricks and mortar") and defines the principal permeation barrier in the skin [3]. For an excellent review of the many facets of this subject, see Schaefer and Redelmeier [4].

There are three pathways for the penetration of compounds through the stratum corneum: appendageal, transcellular, and intercellular [5,6]. These are not mutually exclusive, and the relative importance of each for any given compound will depend on the area and permeability of the pathways. Evidence suggests that the intercellular lipid domain constitutes the principal permeation pathway for many compounds [7–12].

At a phenomenological level, transport of drug through the stratum corneum can be described by a one-dimensional diffusion equation:

$$\partial C/\partial t = D \cdot \partial^2 C/\partial x^2 \tag{1}$$

where C is the drug concentration, D is its diffusion coefficient, and x is the spatial dimension. This equation can be solved using the boundary conditions that can be approximated experimentally: a fixed drug concentration at the external surface of the skin and zero concentration on the internal face. The steady-state flux of drug-per-unit-area of stratum corneum, J, is then given by:

$$J = D \cdot K \cdot C_v/L \tag{2}$$

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Summary of Advantages of Transdermal Therapy

Functional capability	Corresponding therapeutic or other advantages[a]
Prolonged therapy after one application/multiday, continuous drug delivery	Reduces dosing frequency Improves patient compliance Enables use of short-half-life drugs due to sustained therapeutic effect Provides more consistent treatment of chronic disease
Improved drug absorption due to avoidance of GI tract	Facilitates more predictable drug absorption due to avoidance of GI tract variables (pH, motility, transit time, presence of food) Hepatic first-pass effect Reduces dose for some drugs Provides alternative when oral dosing is unsuitable (e.g., in nauseated or unconscious patients)
Noninvasive parenteral route	Advantages over invasive administration Lower risk of complications More convenient Painless Suitable for outpatient use No transmission of blood-borne diseases
Controlled drug input[b]	Minimizes peaks and troughs in blood drug concentration Drug concentrations in blood controlled to provide: Sustained therapeutic action Abatement of side effects
Ease of use	Removed easily, permitting termination of dosing Suitable for medicating unconscious or nauseated patients Reduces need for office visits Reduces overall treatment costs in many instances
Retrievable dosage form	Cessation of drug input if necessary[c]

[a] Not all advantages will apply to all transdermal dosage forms.
[b] Applies only to controlled-release dosage forms.
[c] Decline of drug concentrations in plasma depends on depletion of drug depot (if any) in skin and drug half-life.

Copyright © 2003 Marcel Dekker, Inc.

where K is the drug partition coefficient between vehicle and stratum corneum, and C_v is the drug concentration in the vehicle. This equation allows determination of the effective thickness of the stratum corneum, L, which is found to be approximately three orders of magnitude greater than the physical thickness [13]. Thus, the diffusive pathways through the stratum corneum are highly tortuous.

C. Development Status

1. Available Types

While transdermal drug delivery systems currently on the market display a wide array of designs, D-TRANS® transdermal therapeutic systems consist of two basic types: membrane-controlled and matrix. A schematic of these designs is shown in Figure 1.

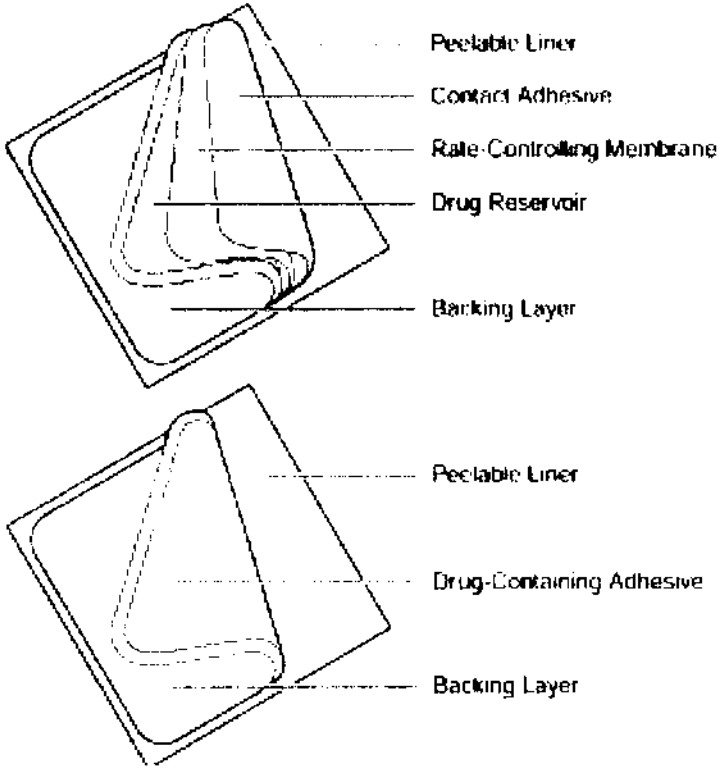


Figure 1 Schematics of two transdermal drug delivery system designs: (A) membrane-controlled and (B) matrix.

Copyright © 2003 Marcel Dekker, Inc.

a. Membrane-Controlled Systems These systems consist of a backing layer, a drug reservoir, a rate-controlling membrane, and an adhesive covered by a peelable liner. The drug reservoir may consist of drug in either liquid or gel form, which is referred to as form-fill-seal (FFS), or the drug may be dispersed in a polymeric material. Examples of membrane-controlled, FFS systems include the ALZA-developed D-TRANS® products Duragesic® and Testoderm-TTS® for the delivery of fentanyl and testosterone, respectively.

b. Matrix Systems These systems contain a backing layer, a polymeric drug reservoir, an adhesive, and a peelable liner. In some cases, the system contains only the backing layer and the drug in the adhesive, which is covered by a peelable liner. Matrix systems currently marketed include ALZA-developed D-TRANS® product Testoderm®, 3M Pharmaceuticals' Climara® for the delivery of 17β-estradiol, and Elan's nicotine delivery system Prostep®.

Matrix systems are desirable because their simplicity reduces manufacturing costs, and their thinner system profile may allow greater comfort during wearing. However, formulation challenges are greatest with this design, especially in the drug-in-adhesive systems, as the adhesive must serve multiple functions including housing the drug and controlling its release while maintaining adhesion to the skin [14].

2. System Design

The choice of D-TRANS® design for a given drug depends on several factors, including the solubility and stability of the drug and excipients in the various components, and the release kinetics of the drug from the device and through the skin. If a drug is transported across skin at a rate that is faster than desired, control of the delivery rate must be accomplished by the system. For example, a rate-controlling membrane is used in the Nicoderm®CQ® system to reduce the transport of nicotine across skin by approximately ninefold. In contrast, skin-controlled delivery occurs if a drug is transported across skin slower than it is transported through the system. In this case, the rate of delivery of drug from the device is less critical, and a wider array of system designs becomes available [15].

D. Marketed Products

To date, ALZA has developed nine transdermal systems based on the D-TRANS® technology: Testoderm-TTS®, Testoderm®, Testoderm® with Adhesive, Transderm Scop®, Transderm-Nitro®, NicoDerm®CQ®, Duragesic®, Estraderm®, and Catapres TTS®. Table 2 lists these products and the seven drugs that are delivered by the systems. Some of these drugs have also been developed as transdermal products by other companies including TheraTech (now Watson), 3M Pharma-

Copyright © 2003 Marcel Dekker, Inc.

Table 2 ALZA D-TRANS® Systems and Their Components

Product name and drug	System type	Backing layer	Drug reservoir	Rate-controlling membrane	Adhesive	Peelable liner
Testoderm-TTS® (non-scrotal) (testosterone)	Membrane-controlled FFS	Transparent polyester, EVA copolymer	Hydroxypropyl cellulose, ethanol, testosterone	EVA copolymer	PIB, mineral oil	Silicone-coated polyester
Testoderm® (scrotal) (testosterone)	Matrix	Polyester	EVA copolymer, testosterone	—	—	Silicone-coated polyester or fluorocarbon diacrylate-coated polyester
Testoderm® with Adhesive (scrotal) (testosterone)	Matrix, striped adhesive	Polyester	EVA copolymer, testosterone	—	PIB	Silicone-coated polyester or fluorocarbon diacrylate-coated polyester
Transderm Scop® (scopolamine)	Membrane-controlled	Tan-colored polyethylene, aluminized polyester, EVA copolymer	PIB, mineral oil, scopolamine	Microporous polypropylene	PIB, mineral oil, scopolamine	Silicone-coated polyester

Copyright © 2003 Marcel Dekker, Inc.

Transderm-Nitro®/ Transiderm-Nitro® (nitroglycerin)	Membrane-controlled FFS	Tan-colored polyethylene, aluminized polyester, EVA copolymer	Silicone fluid, nitroglycerin, lactose triturate	EVA copolymer	Silicone	Fluorocarbon diacrylate-coated polyester
NicoDerm® CQ®/NiQuitin® CQ® (nicotine)	Membrane-controlled	Tan-colored polyethylene, aluminized polyester, EVA copolymer OR transparent polyester, EVA copolymer	EVA copolymer, nicotine	Polyethylene	PIB	Silicone-coated polyester
Duragesic®/ Durogesic® (fentanyl)	Membrane-controlled FFS	Transparent polyester, EVA copolymer	Hydroxyethyl cellulose, ethanol, fentanyl	EVA copolymer	Silicone	Fluorocarbon diacrylate-coated polyester
Estraderm® (17β-estradiol)	Membrane-controlled FFS	Transparent polyester, EVA copolymer	Hydroxyethyl cellulose, ethanol, estradiol	EVA copolymer	PIB, mineral oil	Silicone-coated polyester
Catapres-TTS® (clonidine)	Membrane-controlled	Tan-colored polyethylene, aluminized polyester, EVA copolymer	PIB, mineral oil, colloidal silicon dioxide, clonidine	Microporous polypropylene	PIB, mineral oil, colloidal silicon dioxide, clonidine	Silicone-coated polyester or fluorocarbon diacrylate-coated polyester

FFS, form-fill seal; EVA, ethylene-vinyl acetate; PIB, polyisobutylene.

Copyright © 2003 Marcel Dekker, Inc.

ceuticals, Noven, Cygnus, Elan, Lohman Neuwied, Searle and Key Pharmaceutical.

III. D-TRANS® TECHNOLOGY SYSTEM COMPONENTS

System components must be physically and chemically stable and should not adversely impact the stability of the drug or other formulation excipients. They should also exhibit acceptable compatibility with the skin and be easily modified to allow tailoring of properties for the delivery of different drugs. General considerations for the requirements for transdermal system components are discussed below under the respective headings. Table 2 lists the specific components used in currently marketed ALZA-developed systems.

A. Drug

The selection of drug candidates is based primarily on the biological and physicochemical properties of the drug [16]. Criteria that are typically used for selection include:

Parenteral dose less than 20 mg/day
Short half-life (requiring multiple daily doses in current dosage form)
Acceptable skin toxicity (little or no skin irritation or sensitization)
Molecular weight less than 500 Daltons
Log octanol-water partition coefficient of approximately 0–3
Solubility in mineral oil and water greater than 1 mg/mL

B. Drug Reservoir

Both liquid and solid materials have been used as drug reservoirs in transdermal delivery. Liquids such as ethanol and silicone fluid are used in the membrane-controlled FFS systems. Polymers such as polyisobutylene, silicone elastomers, and polyvinyl alcohol/polyvinyl pyrrolidone blends have been used in other systems. Cosolvents may be added as needed to increase drug solubility [17]. The partition and diffusion of drugs through polymers is affected primarily by glass transition temperature, molecular weight, and functional groups on the polymer. Modification of polymer properties and thus of drug release rate may be achieved by varying polymer cross-linking or chemical structure (as with copolymers), use of polymer blends, and addition of plasticizers [15].

C. Rate-Controlling Membranes

Drug release through rate-controlling membranes (RCMs) may also be modified by varying the membrane polymer properties, as discussed above. For example,

Copyright © 2003 Marcel Dekker, Inc.

microporous polypropylene and ethylene-vinyl acetate copolymers are used as RCMs in several D-TRANS® products. In the latter case, drug permeation rates can be altered by changing vinyl acetate content and membrane thickness [18]. For the Duragesic® system, the vinyl acetate content in the RCM is selected to achieve the desired transport of ethanol, which in part controls the transport of fentanyl across the skin.

D. Pressure-Sensitive Adhesives

A pressure-sensitive adhesive is required to adhere the transdermal device to the body. Itching, irritation, residue remaining on removal, and trauma to the skin upon removal must all be minimized. In a membrane-controlled device, the drug is required to diffuse from the drug reservoir through the adhesive while maintaining adequate adhesion to the skin. In a drug-in-adhesive matrix device, the pressure-sensitive adhesive contains all of the dissolved or dispersed drug and excipients. Thus, the solubility and stability of the drug/excipients in the adhesive and their effect on adhesion are critical issues that must be addressed during adhesive selection. Commercially available materials for transdermal use include the polyisobutylene-, polyacrylate-, and polysiloxane-based adhesives. Adhesive requirements, testing, and properties of the three classes of pressure-sensitive adhesives have been reviewed extensively by Venkatraman and Gale [14].

E. Penetration Enhancers

A major impediment to transdermal drug delivery is the low percutaneous permeability of many drugs, preventing effective dosing from a patch of acceptable size. In some cases, however, chemical permeation enhancers permit alteration of the structure and dynamics of the stratum corneum so that adequate drug permeability can be achieved. A wide variety of compounds have been studied for use as permeation enhancers, including homologous series of aliphatic alcohols, fatty acids and their esters, ionic and nonionic surfactants of many kinds, and essential oils [19]. A permeation enhancer can increase the solubility of a drug or the diffusivity of a drug in the stratum corneum. For example, experimental evidence generated at ALZA suggests that ethanol operates by the former mechanism, while glyceryl laurate operates by the latter. However, any particular enhancer may work by a combination of effects.

F. Backing Membranes and Peelable Liners

Backing membranes have different requirements depending upon the system design in which they are used. In general, however, all backing membranes must exhibit a low moisture vapor transmission rate and have suitable mechanical properties (e.g., flexibility and tensile strength) for both wearing on the skin and han-

Copyright © 2003 Marcel Dekker, Inc.

dling during manufacturing. Some membrane-controlled systems also require heat-sealable backing membranes. Polyolefins, multilayered films, polyesters, and elastomers in clear, pigmented, or metallized form are commonly used [17]. Peelable liners are usually composed of similar materials (e.g., polyethlene, polyesters) coated with a release layer of silicone or fluorocarbon agents.

IV. TECHNIQUES FOR MEASURING SKIN PERMEATION

A number of in vitro and in vivo methods are used to determine the extent and rate of percutaneous absorption of drugs. These methods as well as various permeability models are used to predict absorption in humans [18,20–23].

A. In Vitro Testing

Diffusion cells made of glass or other nonreactive and drug-compatible materials with donor and receptor compartments separated by excised human or animal skin are most often used for the assessment of skin permeation in vitro [24,25]. Since in vitro methods allow the investigator to control for various experimental factors that influence percutaneous absorption, they are valuable for screening. Therefore, efforts are made to duplicate the general behavior of living tissue in situ by careful selection of experimental conditions and diffusion cell design [24,26]. In vitro methods are also employed to monitor formulation effects on drug release and to ensure batch-to-batch uniformity [27,28].

B. In Vivo Methods

Pharmacokinetic methods are most often used for measuring in vivo permeation. After application of drug to the skin, the measured serum or plasma concentrations and the predetermined clearance rate of the compound are used to calculate the transdermal permeation rate [29]. Alternatively, the amount of drug remaining in the system after a given time period can be measured, and the difference between the residual drug and the dose initially applied is assumed to represent the amount of drug that permeated the skin and was absorbed into the systemic circulation. Other methods of determining skin permeation in vivo include the use of a topically applied radiolabeled compound [30,31], infrared spectroscopy [32–34], microdialysis [35], and a laser-photoacoustic method for percutaneous absorptiometry [36].

C. Human In Vitro/In Vivo Correlation

The transdermal in vivo and in vitro flux values for 18 drugs are plotted on a logarithmic scale in Figure 2. The drug compounds exemplified all have molecu-

Copyright © 2003 Marcel Dekker, Inc.

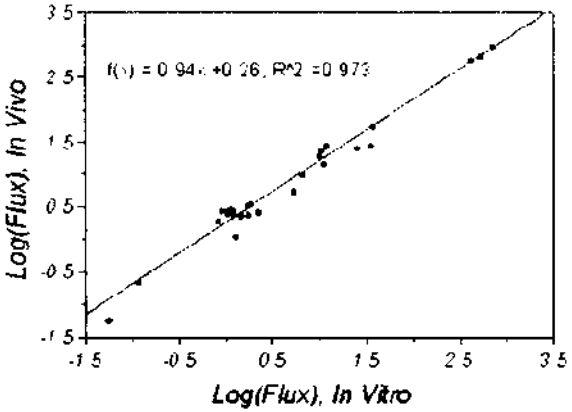


Figure 2 Correlation between human in vivo and in vitro transdermal drug flux. Each data point represents a different drug. Dashed line indicates the best fit through the data points.

lar weights less than 800 Daltons. As illustrated in Figure 2, the in vitro and in vivo flux values can be correlated over several orders of magnitude. However, in general, in vitro flux values underestimate in vivo values.

D. Animal Models

Because of the potential toxicity of many compounds, percutaneous absorption studies must be conducted in animals prior to testing in humans. However, most animals available for experimental use differ significantly from humans in ways that impact transdermal permeation, including the thickness and lipid composition of the stratum corneum and the density of hair follicles and sweat glands [37]. Investigators have compared the percutaneous absorption of several compounds in a number of animal models [38]. In general, the comparative in vivo data indicate that percutaneous absorption in the pig and primate are most similar to that in humans, while rodent skin is generally more permeable than human skin.

V. PRECLINICAL DEVELOPMENT

First-to-market transdermal systems are regulated as new chemical entities (NCEs) by the U.S. Food and Drug Administration (FDA) and require standard nonclinical testing for market approval [39]. This includes subchronic, chronic,

Copyright © 2003 Marcel Dekker, Inc.

carcinogenic, and mutagenic assays that provide a complete toxicology profile on compounds delivered transdermally. Phototoxicity and skin metabolism studies may also be required [40]. However, the nonclinical requirements are generally reduced for transdermal systems that utilize components that have been previously used in other dermal applications or drugs that have been approved in other dosage forms. Skin irritation and sensitization studies are the primary focus in assessing transdermal systems. Toxicology methods specific to transdermal delivery systems have been discussed at length by Prevo et al. [39].

A. Irritation Studies

Irritation, the local inflammatory response of normal living skin to direct injury by single, repeated, or prolonged contact with a chemical agent, is observed macroscopically as erythema and edema. Compounds are grouped according to their irritant properties using acute and subchronic irritation testing. The methods described by Draize et al. constitute the most standardized procedures for this evaluation [41]. Organ and cell cultures are also used to predict whether the application of a compound will result in damage to keratinocytes or to other types of cells. Cytotoxicity is assessed by end-points such as cell growth, enzyme release, release of radioactive markers, exclusion of dyes, metabolism, and plating efficiency [42,43].

B. Sensitization Studies

Contact sensitivity is characterized by cell-mediated (thymocyte) allergic reactions of the skin. It may occur after the first exposure or may require repeated exposure to the sensitizer, with or without potentiation by physical or chemical irritants or immunopotentiators [44,45]. Predictive testing can readily identify drugs or other transdermal system components that are capable of producing sensitization [46]. The hairless guinea pig is the most widely used model for these studies because of the genetically based predisposition of this species to sensitization [46–48]. Sensitization potential may also be evaluated by assay of the lymphokines released by antigens from sensitized lymphocytes and lymphocyte proliferation assays such as the murine lymph node assay [49,50].

VI. CLINICAL ASSESSMENT

To highlight specific clinical advantages provided by transdermal drug delivery, a few examples are provided below of clinical results obtained with some of the ALZA-developed D-TRANS® systems as well as other transdermal products.

Fentanyl, an opioid analgesic, is delivered over a period of 72 h from Duragesic® fentanyl transdermal system (marketed by Janssen Pharmaceutica, Titus-

Copyright © 2003 Marcel Dekker, Inc.

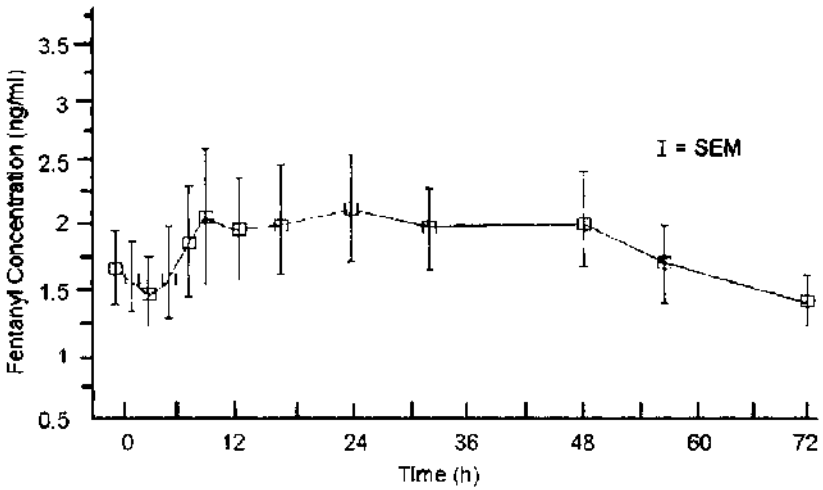


Figure 3 Mean serum fentanyl concentrations obtained from eight patients following application of a Duragesic 75 μg/h system.

ville, NJ) for the treatment of chronic pain. Use of the Duragesic® system results in constant fentanyl blood concentrations over a prolonged time period, as shown in Figure 3. Several clinical trials have demonstrated analgesic activity of transdermal fentanyl in patients with severe pain [51,52].

Oral estrogens undergo extensive hepatic and gut wall first-pass metabolism [53]. Because of this presystemic inactivation, the plasma concentration of the pharmacologically inactive metabolite estrone increases with respect to estradiol. Following transdermal delivery, first-pass metabolism of estradiol is avoided and the estrone/estradiol ratio is maintained close to unity, similar to the physiological ratio observed in premenopausal women [54].

Clonidine, a potent antihypertensive, is delivered transdermally by the once-a-week Catapres-TTS® (marketed by Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT). Several studies have demonstrated that transdermal clonidine effectively reduces blood pressure in patients with mild-to-moderate hypertension [55]. When transdermal therapy was compared with oral delivery of clonidine, efficacy was similar for the two delivery modalities. However, side effects such as drowsiness and dry mouth occurred less frequently in patients treated with transdermal clonidine [56].

Transdermal systems usually require less frequent dosing when compared with their oral counterparts. In a clinical study involving transdermal estradiol, patient compliance was rated excellent, as 90% of patients ($n = 114$) did not miss a single drug application in 12 months [57]. Similarly, Polvani et al. [58] reported that in a randomized comparative study of the clinical evaluation of

Copyright © 2003 Marcel Dekker, Inc.

hormone replacement by transdermal and oral routes, the patients treated with transdermal estradiol showed better compliance and fewer patients dropped out of the study.

VII. MANUFACTURING

Generally accepted processes for production of transdermal delivery systems of the varying designs include material dissolution in a solvent, followed by casting/drying and lamination of desired layers of the system. Subsequent processes include die cutting and packaging of the final product for lot-clearance testing and distribution. Statistically based designed experiments are used to define the optimum processing parameters and the process capabilities.

Today, the issues facing D-TRANS® manufacturing arise from efforts to find a balance between manufacturing costs and efficiencies and maintaining the integrity of the formulation. In this arena, two major manufacturing processes are contending. Solvent casting methods are generally conducted at lower temperatures and therefore are preferred for temperature-labile formulations. Extrusion methods, while more efficient and less costly, are generally conducted at higher temperatures and with high shear stress levels. Therefore, extrusion methods cannot always be employed with sensitive formulations.

VIII. OUTLOOK

While the simultaneous administration of multiple compounds via transdermal delivery is possible today, all of the existing transdermal systems follow simple zero-order kinetics for the input of drugs. The design and manufacture of transdermal systems containing complex formulations allowing for other dosing profiles would require additional research. In addition, extensive formulation development activities are also needed to explore new permeation enhancers and excipients to facilitate the delivery of more-difficult-to-deliver drugs, higher doses of low-molecular weight compounds, and high-molecular-weight drug entities including peptides and proteins without the elicitation of undesirable cutaneous side effects.

ACKNOWLEDGMENTS

The authors wish to acknowledge Karen Getz, Rod Panos, Mary Prevo, and Mary Southam of ALZA Corporation for their help in preparing the chapter.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. JE Shaw, SK Chandrasekaran. Controlled topical delivery of drugs for systemic action. Drug Metab Rev 8:223–233, 1978.
2. AF Kydonieus. Fundamentals of transdermal drug delivery. In: AF Kydonieus, B Berner, eds. Transdermal Delivery of Drugs. Vol. 1. Boca Raton, FL: CRC Press, 1987, pp. 3–16.
3. SK Chandrasekaran, JE Shaw. Factors influencing the percutaneous absorption of drugs. Curr Probl Dermatol 7:142–155, 1978.
4. H Schaefer, TE Redelmeier. Skin Barrier: Principles of Percutaneous Permeations. Basel: Karger, 1996, pp. 1–85.
5. BW Barry. The LPP theory of skin penetration enhancement. In: RL Bronaugh, HI Maibach, eds. In Vitro Percutaneous Absorption: Principles, Fundamentals, and Applications. Boca Raton, FL: CRC Press, 1991, pp. 165–185.
6. A Rolland, N Wagner, A Chatelus, B Shroot, H Schaefer. Site-specific drug delivery to pilosebaceous structures using polymeric microspheres. Pharm Res 10:1738–1744, 1993.
7. PM Elias. Epidermal lipids, barrier function, and desquamation. J Invest Dermatol 80(suppl):44s–49s, 1983.
8. RO Potts, ML Francoeur. The influence of stratum corneum morphology on water permeability. J Invest Dermatol 96:495–499, 1991.
9. GL Flynn. Physicochemical determinants of skin absorption. In: TR Garrity, CL Henry, eds. Principles of Route-to-Route Extrapolations for Risk Assessment. New York: Elsevier, 1990, pp. 93–127.
10. RO Potts, ML Francoeur. Lipid biophysics of water loss through the skin. Proc Natl Acad Sci USA 87:3871–3873, 1990.
11. N Kitson, J Thewalt, M Lafleur, M Bloom. A model membrane approach to the epidermal permeability barrier. Biochemistry 33:6707–6715, 1994.
12. RJ Scheuplein, IH Blank. Permeability of the skin. Physiol Rev 51:702–747, 1971.
13. S Mitragotri. In situ determination of partition and diffusion coefficients in the lipid bilayers of stratum corneum. Pharm Res 17:1026–1029, 2000.
14. S Venkatraman, R Gale. Skin adhesives and skin adhesion. 1. Transdermal drug delivery systems. Biomaterials 19:1119–1136, 1998.
15. RW Baker, J Heller. Materials selection for transdermal delivery systems. In: J Hadgraft, RH Guy, eds. Transdermal Drug Delivery. New York: Marcel Dekker, 1989, pp. 293–311.
16. RH Guy, J Hadgraft. Selection of drug candidates for transdermal drug delivery. In: J Hadgraft, RH Guy, eds. Transdermal Drug Delivery. New York: Marcel Dekker, 1989, pp. 59–81.
17. GA Patani, YW Chien. Transdermal drug delivery devices: system design and composition. In: J Swarbrick, JC Boylan, eds. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker, 1999, pp. 309–337.
18. AS Michaels, PSL Wong, R Prather, RM Gale. A thermodynamic method of predicting the transport of steroids in polymer matrices. Am Inst Chem Eng J 21:1073–1080, 1975.

Copyright © 2003 Marcel Dekker, Inc.

19. KA Walters. Penetration enhancers and their use in transdermal therapeutic systems. In: J Hadgraft, RH Guy, eds. Transdermal Drug Delivery. New York: Marcel Dekker, 1989, pp. 197–246.
20. G Cleary. Transdermal delivery systems: a medical rationale. In: V Shah, H Maibach, eds. Topical Drug Bioavailability, Bioequivalence and Penetration. New York: Plenum Press, 1993, pp. 17–68.
21. HY Ando, TW Schultz, RL Schnaare, ET Sugita. Percutaneous absorption: a new physicochemical predictive model for maximum human in vivo penetration rates. J Pharm Sci 73:461–467, 1984.
22. EJ Lien, H Gao. QSAR analysis of skin permeability of various drugs in man as compared to in vivo and in vitro studies in rodents. Pharm Res 12:583–587, 1995.
23. R Gale, J Hunt, ME Prevo. Transdermal drug delivery, passive. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. New York: J Wiley & Sons, 1999, pp. 975–991.
24. CL Gummer, HI Maibach. Diffusion cell design. In: RL Bronaugh, HI Maibach, eds. In Vitro Percutaneous Absorption: Principles, Fundamentals and Applications. Boca Raton, FL: CRC Press, 1991, pp. 8–16.
25. JP Skelly, VP Shah, HI Maibach, RH Guy, RH Wester, GL Flynn, A Yacobi. FDA and AAPS report of workshop on principles and practices of in vitro percutaneous penetration studies: relevance to bioavailability and bioequivalence. Pharm Res 4: 265–267, 1987.
26. SW Collier, RL Bronaugh. Receptor fluids. In: RL Bronaugh, HI Maibach, eds. In Vitro Percutaneous Absorption: Principles, Fundamentals and Applications. Boca Raton, FL: CRC Press, 1991, pp. 31–49.
27. VP Shah, JP Skelly. Practical considerations in developing a quality control (in vitro release) procedure for topical drug products. In: VP Shah, HI Maibach, eds. Topical Drug Availability, Bioequivalence, and Penetration. New York: Plenum Press, 1993, pp. 107–116.
28. USP 24. Transdermal delivery systems, general drug release standards. In: US Pharmacopeia and National Formulary. Rockwell, MD: United States Pharmacopeial Convention, 1999, pp. 1947–1951.
29. S Gupta, M Southam, R Gale, SS Hwang. System functionality and physiochemcial model of fentanyl transdermal system. J Pain Symptom Manage 7:S17–S26, 1992.
30. A Rougier, D Dupuis, C Lotte, R Roguet, H Schaefer. In vivo correlation between stratum corneum reservoir function and percutaneous absorption. J Invest Dermatol 81:275–278, 1983.
31. A Rougier, D Dupuis, C Lotte, R Roguet, RC Wester, HI Maibach. Regional variation in percutaneous absorption in man: measurement by the stripping method. Arch Dermatol Res 278:465–469, 1986.
32. VH Mak, RO Potts, RH Guy. Percutaneous penetration enhancement in vivo measured by attenuated total reflectance infrared spectroscopy. Pharm Res 7:835–841, 1990.
33. B Sennhenn, K Giese, K Plamann, N Harendt, K Kolmel. In vivo evaluation of the penetration of topically applied drugs into human skin by spectroscopic methods. Skin Pharmacol 6:152–160, 1993.
34. N Higo, A Naik, DB Bommannan, RO Potts, RH Guy. Validation of reflectance

Copyright © 2003 Marcel Dekker, Inc.

infrared spectroscopy as a quantitative method to measure percutaneous absorption in vivo. Pharm Res 10:1500–1506, 1993.
35. C Anderson, T Andersson, M Molander. Ethanol absorption across human skin measured by in vivo microdialysis technique. Acta Derm Venereol 71:389–393, 1991.
36. R Takamoto, R Namba, M Matsuoka, T Sawada. Human in vivo percutaneous absorptiometry using the laser-photoacoustic method. Anal Chem 64:2661–2663, 1992.
37. PM Elias, ER Cooper, A Korc, BE Brown. Percutaneous transport in relation to stratum corneum structure and lipid composition. J Invest Dermatol 76:297–301, 1981.
38. MJ Bartek, JA LaBudde, HI Maibach. Skin permeability in vivo: comparison in rat, rabbit, pig and man. J Invest Dermatol 58:114–123, 1972.
39. M Prevo, M Cormier, K Nichols. Predictive toxicology methods for transdermal delivery systems. Toxicol Meth 6:83–98, 1996.
40. T Maurer, EG Weirich, R Hess. Predictive animal testing for photocontact allergenicity. Br J Dermatol 103:593–605, 1980.
41. JH Draize, G Woodard, HO Calvery. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 82:377–390, 1944.
42. A Bulychev, A Trouet, P Tulkens. Uptake and intracellular distribution of neutral red in cultured fibroblasts. Exp Cell Res 115:343–355, 1978.
43. T Mosmann. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods 65:55–63, 1983.
44. EV Buehler. Occlusive patch method for skin sensitization in guinea pigs: the Buehler method. Food Chem Toxicol 32:97–101, 1994.
45. AM Kligman. The identification of contact allergens by human assay. 3. The maximization test: a procedure for screening and rating contact sensitizers. J Invest Dermatol 47:393–409, 1966.
46. G Klecak. Test methods for allergic contact dermatitis in animals. In: FN Marzulli, HI Maibach, eds. Dermatotoxicology. 5th ed. Washington, DC: Taylor & Francis, 1996, pp. 437–459.
47. DF Woodward, AL Nieves, LA Williams, CA Spada, SB Hawley, JL Duenes. A new hairless strain of guinea pig: characterization of the cutaneous morphology and pharmacology. In: HI Maibach, NJ Lowe, eds. Models in Dermatology. Basel: Karger, 1989, pp. 71–78.
48. AE Chester, TG Terrell, E Nave, AE Dorr, LR Depass. Dermal sensitization study in hairless guinea pigs with dinitrochlorobenzene and ethyl aminobenzoate. J Toxicol Cut Ocul Toxicol 7:273–281, 1988.
49. WE Parish. Evaluation of in vitro predictive tests for irritation and allergic sensitization. Food Chem Toxicol 24:481–494, 1986.
50. I Kimber, RJ Dearman, EW Scholes, DA Basketter. The local lymph node assay: developments and applications. Toxicology 93:13–31, 1994.
51. S Ahmedzai, D Brooks. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manag 13:254–261, 1997.
52. R Payne, SD Mathias, DJ Pasta, LA Wanke, R Williams, R Mahmoud. Quality of

Copyright © 2003 Marcel Dekker, Inc.

life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. J Clin Oncol 16:1588–1593, 1998.
53. S Campbell, MI Whitehead. Potency and hepato-cellular effects of estrogen after different routes of administration. In: PA Van Keep, PA Utian, A Vermeulen, eds. The Controversial Climacteric. Lancaster: MTP Press, 1982, pp. 103–125.
54. RJ Chetkowski, DR Meldrum, KA Steingold, D Randle, JK Lu, P Eggena, JM Hershman, NK Alkjaersig, AP Fletcher, HL Judd. Biological effects of transdermal estradiol. N Engl J Med 314:1615–1620, 1986.
55. S Popli, JT Daugirdas, JA Neubauer, B Hockenberry, JE Hano, TS Ing. Transdermal clonidine in mild hypertension: a randomized, double-blind, placebo-controlled trial. Arch Intern Med 146:2140–2144, 1986.
56. TR MacGregor, KM Matzek, JJ Keirns, RG van Wayjen, A van den Ende, RG van Tol. Pharmacokinetics of transdermally delivered clonidine. Clin Pharmacol Ther 38:278–284, 1985.
57. AWHM Lutkie, S Hackel, LLM van de Ven. Long-term tolerability and efficacy of Fem7, a once-weekly transdermal system, in women with post-menopausal complaints. J Clin Res 1:161–171, 1998.
58. F Polvani, L Zichella, A Bocci, F Bottiglioni, G Cagnazzo, C Campagnoli, L Carenza, S Cianci, V Danesino, L De Cecco. A randomized comparative study for the clinical evaluation of hormone replacement by transdermal and oral routes. Clin Exp Obstet Gynecol 18:207–213, 1991.

Copyright © 2003 Marcel Dekker, Inc.

41
E-TRANS Technology

J. Bradley Phipps, Rama V. Padmanabhan, Wendy Young, Rod Panos, and Anne E. Chester
ALZA Corporation, Mountain View, California, U.S.A.

I. INTRODUCTION

Electrotransport technology (referred to as E-TRANS® technology at ALZA Corporation, Mountain View, CA) uses an electric potential to provide noninvasive delivery of therapeutic substances across intact skin for local and systemic applications. An electrotransport drug delivery system typically consists of a power supply connected to a pair of electrodes in contact with ionically conductive reservoirs that, in turn, are in contact with the skin. Since the rate of drug delivery is proportional to the applied electrical current, electrotransport systems have the potential to provide precise dosing as well as patterned and on-demand delivery.

The earliest reference to the use of an electric potential to enhance the penetration of charged substances into tissues was by Veratti in 1747 [1]. In 1907, Stephane Leduc [2], an important early researcher in the field, described the delivery of ionic substances in *Les Ions et les Medications Ioniques*. Today, commercially available devices are typically bench-top systems with discrete patches connected to a power supply by electrical cables. However, innovations in electronic circuitry and battery technology have enabled administration of electrotransport treatments with small, integrated patch-like systems.

II. THEORY AND MECHANISM OF ELECTROTRANSPORT

The term "electrotransport" describes the general process of electrically assisted transport, thus encompassing several processes for moving molecules across the skin: electromigration, electroosmosis, and electroporation. For any given elec-

Copyright © 2003 Marcel Dekker, Inc.

trotransport treatment, one or more of these processes may occur simultaneously and to a varying extent, depending on the magnitude and duration of the applied electric field, the composition of the donor reservoir, and the type of the tissue being treated. Electromigration, the movement of charged ionic species in response to an applied electric field, is usually of primary importance for delivering charged drugs [3]. This process is commonly called iontophoresis in the medical literature.

The rate of transport of charged drug substances across the skin is expressed by the Nernst-Planck equation, which contains terms for diffusion, electromigration, and bulk convection. Under optimized conditions, however, the contribution of electromigration is often much greater than that of the other two, so the expression for delivery of a drug species is frequently simplified to include only the electromigration term [4]. The mass transport of drug is thus related to the electric current, according to Faraday's principle:

$$N = (t_d IM)/(z_d F) \tag{1}$$

where:

N = total rate of delivery (mol/s)
t_d = transport number (the fraction of charge carried by the drug)
I = current applied across the skin
M = molecular weight
z_d = charge of the drug molecule
F = Faraday's constant

Experimental data have shown that the rate of delivery is linearly proportional to the applied current over a wide range of currents [5]. Thus, for a fixed drug formulation, t_d is a constant. However, the transport number is unique for each drug and is a function of the drug's mobility, charge, and concentration, as compared with those of other migrating species.

$$t_d = \frac{\mu_d |z_d| \; C_d}{\sum_i \mu_i |z_i| C_i} \tag{2}$$

Other migrating species include those ions in the formulation with the same sign of charge as the drug (i.e., competing co-ions), as well as those ions in the body that have the opposite sign as the drug (competing counterions). The transport number determines delivery efficiency, i.e., the amount of drug delivered per unit charge passed across the skin (for a more complete discussion, see Ref. [4]).

A schematic of a typical transdermal electrotransport system is shown in Figure 1. A source of electrical energy, such as a battery, supplies electric current to the body through two electrodes. The first, or donor, electrode delivers the therapeutic agent into the body. The second, or counter, electrode closes the elec-

Copyright © 2003 Marcel Dekker, Inc.

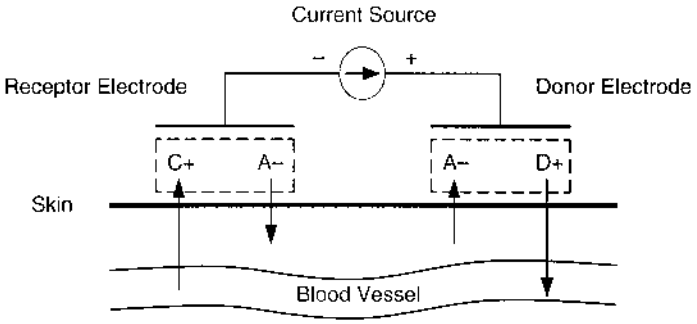


Figure 1 Schematic diagram of an electrotransport device on skin indicating the flow of ions in response to an applied voltage.

trical circuit. Each electrode is placed in contact with its associated ionically conductive reservoir, normally present as a hydrogel. The reservoirs are placed in contact with the patient's skin and contain either the drug (for the donor electrode assembly) or a pharmacologically inactive electrolyte (for the counter electrode assembly).

III. RATIONALE FOR DEVELOPMENT OF E-TRANS® TECHNOLOGY

Several companies market electrotransport products that use essentially the same controller and a few different-sized drug reservoirs/electrode assemblies for topical delivery of different drugs. The Phoresor® Iontophoretic Drug Delivery System (Iomed, Inc., Salt Lake City, UT) and the Dupel® System (Empi Corp., Minneapolis, MN) deliver lidocaine as a local anesthetic and dexamethasone for treatment of local inflammation. The widespread use of these products, especially outside supervised care settings, is limited because of their high initial cost and complex operation. Diagnostic applications of electrotransport have also been commercialized. Systems such as the CF Indicator® (Scandipharm, Birmingham, AL) and the Webster Sweat Inducer (Wescor, Inc. Logan, UT) are available for the diagnosis of cystic fibrosis. Iontophoresis has also been used to extract glucose from skin to detect hypo- and hyperglycemia (Cygnus Corp, Redwood City, CA).

Although transdermal electrotransport products for systemic drug delivery are not yet available commercially, the potential medical and economic benefits, especially for delivering new biotechnology compounds, are driving their development. ALZA Corporation is developing E-TRANS® electrotransport drug de-

Copyright © 2003 Marcel Dekker, Inc.

livery technology for use in home- and clinic-based therapies. Applications requiring intermittent or on-demand dosing and fairly rapid onset of action are suitable for E-TRANS® delivery. E-TRANS® systems are being designed as completely integrated products in which the drug and delivery mechanism are packaged together or as quasi-disposable products where the drug compartment is disposable and the batteries and electronics are reusable. The integrated systems approach enables products that are as simple to use as a passive transdermal drug delivery system, potentially enhancing the convenience and market acceptance of electrotransport therapy. A fully integrated E-TRANS® system for delivery of fentanyl for treatment of acute pain is in phase III safety and efficacy trials (see below). The E-TRANS® (fentanyl) system provides a useful example to outline the development status of E-TRANS® technology.

IV. E-TRANS® DESIGN

The design and manufacture of an E-TRANS® system involves many categories of components (e.g., electronic components, electrodes, formulation, outer housing, and means of attachment to skin). These components must be manufactured, stored, and, ultimately, function together to meet therapeutic, functional, and user needs [4]. Figure 2 displays an exploded view of an integrated E-TRANS® system. This chapter will focus on the following component categories.

A. Electronic Components

The electrical control components of an E-TRANS® system (sometimes referred to as a controller) comprise the power source and the control circuitry, including added user-interface features.

1. Power Source

The electrical power source for portable E-TRANS® devices is a battery, which is commercially available in cell voltages from about 1.2 to 3.0 V. If higher voltage is required to overcome the resistance of the skin and achieve the desired current, cells can be combined in series or circuitry can transform the voltage at the cost of drawing a larger current from the battery. Because skin resistance is highest at the start of current application, the initial resistance will determine the system voltage required to drive the desired current into the skin. However, resistance drops quickly, so 10–20 V is usually sufficient to achieve the desired current in a few minutes.

2. Control Circuitry Requirements

A simple field-effect transistor with a feedback resistor can control the current delivered from a battery at a constant value over a wide range of skin resistances.

Copyright © 2003 Marcel Dekker, Inc.

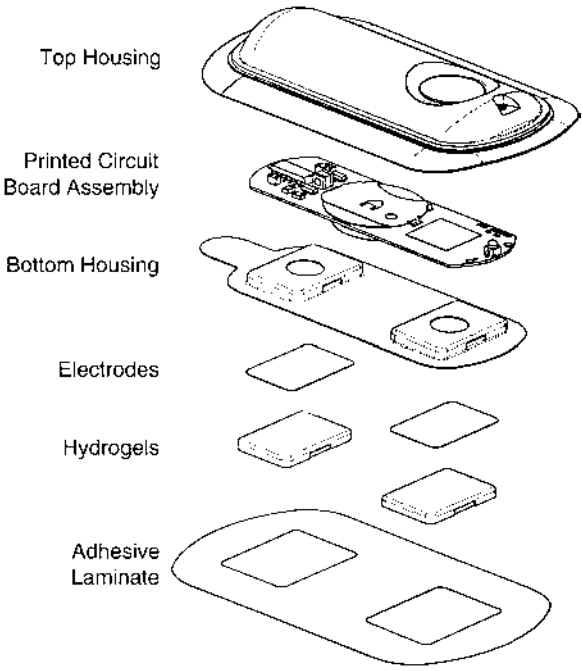


Figure 2 Exploded view of an E-TRANS® system showing major components: top housing, printed circuit board assembly, a bottom housing containing reservoirs for placement of electrodes and hydrogels, and an adhesive laminate. (Diagram from International Patent Publication Number WO 96/39222.)

Some therapies, however, may require varying the applied current in a controlled way to modulate the amount of drug delivered. Circuitry can also be incorporated to increase the reliability and safety of the drug delivery system and provide dosing and system maintenance information to the user [4]. These complex functions can be achieved with microcontrollers or customized application-specific integrated circuits (ASICs) that incorporate both analog and digital circuitry.

B. Electrodes

The electrodes apply an electric field across the skin by converting electric current from the battery into ionic current through the reservoirs, skin, and body. If migration of positively charged species from the delivery reservoir is desired, the donor electrode is the anode, and the counter electrode is the cathode. For negatively charged species, the polarity is reversed.

Copyright © 2003 Marcel Dekker, Inc.

Electrodes can be nonconsumable (made from nonreactive materials) or consumable (containing electroactive species that react during the passage of current). Examples of nonconsumable electrodes include stainless steel or platinum metals. These electrodes may have long lifetimes, but also have significant shortcomings [6,7]. The focus here is on consumable electrodes.

The operation of an electrotransport system necessitates redox reactions at the electrodes in proportion to the amount of charge passed. The reactants and products of the redox reaction need to be managed to meet formulation and biological compatibility requirements. The most commonly used consumable electrodes are based on silver/silver chloride because of their biocompatibility, good performance, and established history of use in medical applications (e.g., electrocardiogram). Other redox couples can have advantages over silver and silver chloride in some circumstances (see Ref. [4] for a discussion).

1. Silver as a Consumable Anode

A silver anode in the presence of chloride or another halide ion in the delivery reservoir is a useful solution for delivering positively charged drugs. Metallic silver oxidizes and in the presence of chloride precipitates as silver chloride. The complete reaction is:

$$Ag^0 + Cl^- \leftrightarrow AgCl^0 + e^- \qquad (E^0 = 0.222\ V) \tag{3}$$

The final product, silver chloride, is electrically neutral and practically insoluble. Therefore, this reaction does not generate species that compete with cationic drugs for delivery. Because the equilibrium potential is low and the reaction is kinetically fast, the silver anode operates at low voltage, avoiding undesirable side reactions such as hydrolysis of water, drug, or excipients. Chloride ion is consumed as it precipitates with silver ions, so sufficient chloride must be present to ensure proper operation of the electrode throughout the therapy. Because the addition of sodium chloride can lead to ion competition and compromise delivery, chloride salts of the drug are preferred [8,9]. Alternative methods to prevent silver migration without introducing mobile cations into the delivery reservoir have been discussed [4].

2. Silver Chloride as a Consumable Cathode

The silver chloride cathode is depicted in Eq. (3) in reverse; silver chloride is reduced to form metallic silver and chloride ion. The silver chloride cathode has many desirable traits: no electrolyte is depleted by its reaction; it is hydrophilic and therefore easily accessible by electrolyte; and the insoluble reaction product, metallic silver, is electrically conductive, eliminating problems of polarization or isolation of the redox species.

Copyright © 2003 Marcel Dekker, Inc.

Reduction of silver chloride releases chloride ions during use, which is not problematic when the electrode is a counterelectrode. However, for donor electrodes, the highly mobile chloride ion can decrease drug flux because of ionic competition. If drug content cannot be increased sufficiently to minimize competition, the chloride ion can be immobilized [4,10].

C. Formulation

The formulation includes the ingredients in the drug and counter reservoirs, which typically consist of a solvent, a drug salt or a biocompatible salt, and a matrix-forming material. A formulation may also include additives such as buffers, antimicrobial agents, antioxidants, and additional electrolyte salts or permeation enhancers; these can interact in a complex fashion to affect rate of delivery, biocompatibility, and product shelf life.

1. Solvent

In addition to the usual considerations of drug solubility, stability, and solvent biocompatibility, the effect of a solvent on the drug charge state is also important. Use of solvents with large dielectric constants results in greater dissociation of the drug salt (i.e., less ion pairing), enhancing drug mobility during application of an electric field. Water is most commonly used because of its large dielectric constant and inherent biocompatibility [11]. Other cosolvents, such as ethanol, glycerol, polyethylene glycol, or polypropylene glycol, may be added to enhance drug solubility and stability, or to reduce the rate of water evaporation [12].

2. Drug Salt

Several unique aspects should be considered when selecting the drug salt for an electrotransport formulation. First, the counterion must be compatible with the electrochemical reactions occurring at the electrode. Halide drug salts are preferable when using a silver anode [4]. In addition, for a particular solvent (e.g., water), selection of a drug salt that more fully dissociates will likely result in more efficient drug delivery. The drug counterion may alter the pH of the interface between the formulation and the skin, altering transport efficiency [13].

3. Matrix

In addition to being biocompatible, the formulation must also be readily incorporated into the system during commercial-scale manufacturing, be easily applied by the user, and leave little or no residue on the skin. Two different matrix-based formulation approaches may achieve these goals. In one approach employing drug-loaded hydrogels, the drug salt is mixed with a solvent and a polar nonioniz-

Copyright © 2003 Marcel Dekker, Inc.

ing polymer and is physically cross-linked [14]. The second approach places drug solution on an absorbent porous material with structural integrity, such as a hydrophilic fabric or hydrophilic porous film. Hydrophilic polymers and/or surfactants have been incorporated into the fabric or foam matrices to improve hydration kinetics and solvent retention [15]. This composite matrix material will readily absorb the drug solution during manufacturing or just before patient use, if needed to ensure drug stability.

4. Excipients

Excipients such as buffers, antimicrobials, antioxidants, and chelating agents may be required for optimal drug stability in electrotransport formulations. Scott and colleagues [4] discuss the various considerations for excipients in electrotransport.

5. Formulation pH

Many drugs have a broad pH range in which drug solubility and stability are adequate for electrotransport delivery. However, optimal drug delivery and biocompatibility are usually restricted to a more narrow pH range. Skin is a permselective membrane with an isoelectric point of about pH 4 [16]. As formulation pH increases, skin becomes more negatively charged, favoring cation transport. To maximize the delivery of a cationic drug, the formulation pH should be as basic as is practical, limited by drug solubility, charge state, stability, and biocompatibility. By analogy, for anionic drugs, acidic formulations are generally preferred. Several investigators have found that formulation pH can also affect skin irritation [13,17,18] (see below).

6. Electrolytes for Counter Reservoir

The electrolyte for the formulation in contact with the counterelectrode must provide sufficient conductivity to minimize the voltage required during system use. The ion delivered from the nondrug formulation must also be biocompatible [19]. Using weak acids and bases as electrolytes for the counterreservoir formulation at the proper pH provides adequate biocompatibility and low skin resistance [17]. Low skin resistance is advantageous since a lower voltage is required from the control circuit, potentially reducing system size and cost if a smaller battery can be used.

V. PRECLINICAL DEVELOPMENT

Preclinical studies with E-TRANS® systems mirror those with passive transdermal systems (see Chapter 40, "D-TRANS® Technology"). Skin irritation is rela-

Copyright © 2003 Marcel Dekker, Inc.

tively common with electrotransport systems, but can be controlled with appropriate choice of electrochemistry, formulation chemistry and electrical delivery parameters (current density, electrode size, and duration of application). Cormier and Johnson [20] found that skin irritation in hairless guinea pigs was reduced by choosing appropriate pH ranges for the anode and cathode formulations. Drug-induced irritation can in some cases be resolved with nonspecific inhibition strategies or by understanding the irritation mechanism [21,22].

VI. IN VIVO/IN VITRO EVALUATION

The in vivo and in vitro electrotransport rates have been obtained for several compounds with differing molecular weights, charges, and solubilities [1,23]. The results demonstrated that (a) in general, reasonable in vitro/in vivo correlations were obtained, and (b) trends observed in vitro were also observed in vivo [24]. Absolute in vivo transport rates for identical formulations under identical conditions could be matched by proper selection of in vitro receptor solution [10].

VII. CLINICAL DEVELOPMENT

Clinical studies have evaluated the pharmacokinetics, tolerance, and clinical utility of E-TRANS® fentanyl for the management of acute pain, such as postoperative pain [25–28]. In a clinical pharmacology study with 12 healthy volunteers blocked by oral naltrexone, intermittent or on-demand fentanyl delivery was evaluated by administering fentanyl for the first 20 min of every hour for 24 h. Serum concentration data during and immediately following the first, thirteenth, and twenty-fifth treatments for 150 μA and 250 μA E-TRANS® treatments and a 50-μg intravenous treatment are shown in Figure 3. Average drug input, mean maximum serum concentration values, and total dose delivered for the E-TRANS® treatment all increased proportionally with current. The study indicated that intermittent or on-demand dosing of fentanyl is feasible and demonstrated that electronically controlled fentanyl delivery from E-TRANS® (fentanyl) provided consistent drug delivery and serum fentanyl concentrations sufficient for analgesia. In safety and tolerance trials, E-TRANS® (fentanyl) was well tolerated both topically and systemically and was clinically useful for the management of acute postoperative pain.

VIII. MANUFACTURING

E-TRANS® (fentanyl), an integrated disposable product, presents a number of manufacturing development and process scale-up issues not common to conven-

Copyright © 2003 Marcel Dekker, Inc.

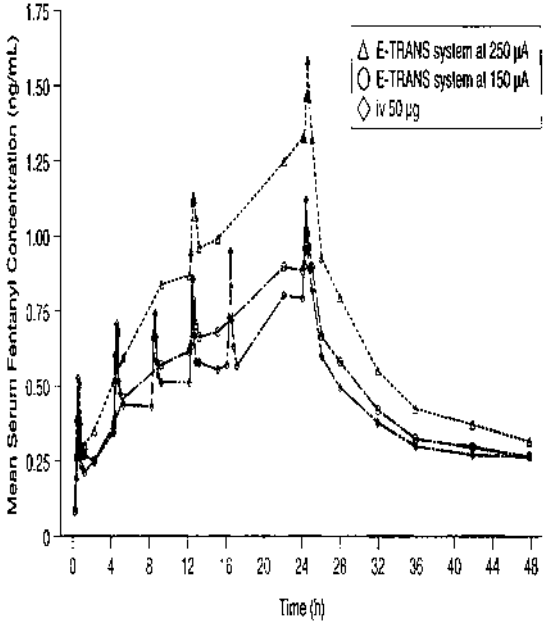


Figure 3 Mean serum fentanyl concentrations for 12 healthy volunteers receiving fentanyl intermittently (20 min each hour over a 24-h administration period) from an E-TRANS® system at two currents, and from an intravenous fentanyl infusion (50 µg for 20 min hourly). (Data from Ref. [26].)

tional pharmaceutical products. This is due to the hybrid character of the E-TRANS® technology, which has both a pharmaceutical component and an electronic/medical device component.

The manufacturing process for E-TRANS® (fentanyl) is primarily an assembly of discrete components interwoven with a drug formulation process. Five major steps comprise the final assembly process: gel formation and mixing, bottom housing assembly, gel curing, joining, and laminating. Process steps involving assembly, joining, and laminating unit operations scale linearly, whereas gel formulating, mixing, and curing steps involve chemical processes and scale nonlinearly. To blend these two characteristic types of processes, the chemical operations are performed as batch processes. The appropriate batch size for the overall finished product was determined by competing factors arising from both sides of this hybrid. The chemical processes present scale limitations, such as gel pot life, while the discrete electronic components present issues of traceability and cost. Therefore, the chemical processes are taken directly to commercial scale

Copyright © 2003 Marcel Dekker, Inc.

in all respects, while the discrete assembly units operations are taken to a commercial production rate, but are demonstrated at only a fraction of commercial volume.

IX. REGULATORY STATUS

In the United States, both integrated E-TRANS® systems and E-TRANS® systems with a reusable controller are regulated as new drugs by the U.S. Food and Drugs Administration under the Center for Drug Evaluation and Research, with device consult by the Center for Devices and Radiological Health. In the European Union, while the integrated E-TRANS® system requires only drug approval, the reusable concept requires both drug and device approvals. The electronic components of an E-TRANS® system must be in conformance with harmonized standards for medical-electronic devices. To comply with medical directives, the systems undergo design verification tests such as electromagnetic interference, electrostatic discharge, and environmental stress tests including shock and vibration tests.

X. OUTLOOK

Electrotransport technology offers a noninvasive alternative to parenteral systemic drug delivery. The electronic control of drug delivery allows rapid onset of action of the drug and makes possible on-demand dosing and patient control as well as patterned, modulated drug delivery. While patient-controlled, on-demand E-TRANS® systems are already under development, electronic control may ultimately lead to closed-loop feedback systems. Polypeptides, proteins, and oligonucleotides may also be candidates for electrotransport [29].

ACKNOWLEDGMENT

The authors wish to acknowledge Deborah S. Waxman for her assistance in the preparation of this chapter.

REFERENCES

1. AK Banga. Electrically Assisted Transdermal and Topical Drug Delivery. Bristol, PA: Taylor & Fransis, 1998.

Copyright © 2003 Marcel Dekker, Inc.

2. S Leduc. Electric Ions and Their Use in Medicine. Liverpool, UK: Rebman Ltd., 1908.
3. RR Burnette. Iontophoresis. In: J Hadgraft, RH Guy, eds. Transdermal Drug Delivery: Development Issues and Research Initiatives. New York: Marcel Dekker, 1989, pp. 247–291.
4. E Scott, JB Phipps, JR Gyory, RV Padmanabhan. Electrotransport systems for transdermal delivery: a practical implementation of iontophoresis. In: Handbook of Pharmaceutical Controlled Release Technology. D. Wise, ed. New York: Marcel Dekker, 2000, pp. 617–659.
5. JB Phipps, RV Padmanabhan, GA Lattin. Ionotophoretic delivery of model inorganic and organic drugs. J Pharm Sci 78:365–369, 1989.
6. P Tyle. Ionotophoretic devices for drug delivery. Pharm Res 3:318–326, 1986.
7. LE Lindblan, L Ekenvall. Electrode material in ionotophoresis. Pharm Res 4:438, 1987.
8. JB Phipps, DF Untereker. Iontophoresis apparatus and methods of producing the same. US patent 4,744,787, 1988.
9. DF Untereker, JB Phipps, GA Lattin. Iontophoretic drug delivery. US patent 5,573,503, 1998.
10. JB Phipps, JR Gyory. Transdermal ion migration. Adv Drug Del Rev 9:137–176, 1992.
11. J Cornish, OI Corrigan, D Foley. The iontophoretic transdermal delivery of morphine hydrochloride and other salts across excised human stratum corneum. In: RC Scott, RH Guy, J Hadgraft, eds. Proceedings of the Conference on Prediction of Percutaneous Penetration: Methods, Measurements, Modeling. International Conference. London: IBC Technical Services, 1990, pp. 302–307.
12. A Jadoul, V Regnier, V Preat. Influence of ethanol and propylene glycol addition on the transdermal delivery by iontophoresis and electroportation. Pharm Res 14: S308–S309, 1997.
13. JE Sanderson, SD Reil, R Dixon. Iontophoretic delivery of non peptide drugs: formulation optimization for maximum skin permeability. J Pharm Sci 78:361–364, 1989.
14. HL Webster. Iontophoresis electrode device with gel insert—has electrode plate in cup-like receptacle so that agar gel disc can protrude for pressing against patient's skin. US patent 4,383,529, 1983.
15. JE Beck, LB Lloyd, TJ Petelenz. Iontophoretic delivery device with integral hydrating means. US patent 5,730,716, 1998.
16. T Rosendahl. Studies on the conducting properties of the human skin to direct current. Acta Physiol Scand 5:130–151, 1942–1943.
17. MJ Cormier, PW Ledger, J Johnson, JB Phipps, S Chao. Reduction of skin irritation and resistance during electrotransport. US patent 5,624,415, 1997.
18. JB Phipps, M Cormier, RV Padmanabhan. In vivo ion efflux from humans and the relationship to skin irritation. In: P Couvreur, D Duchene, P Green, HE Junginger, eds. Transdermal Administration, a Case Study, Iontophoresis. APGI/CRS European Symposium. Paris: Editions de Sante, 1997, pp. 289–291.
19. A Anigbogu, P Singh, P Liu, S Dinh, H Maibach. Effects of iontophoresis on rabbit skin in vivo. Pharm Res 14:S-308, 1997.

Copyright © 2003 Marcel Dekker, Inc.

20. M Cormier, B Johnson. Skin reactions associated with electrotransport. In: P Couvreur, D Duchene, P Green, HE Junginger, eds. Transdermal Administration, a Case Study, Iontophoresis. APGI/CRS European Symposium. Paris: Editions de Sante, 1997, pp. 50–57.
21. M Cormier, PW Ledger, A Amkraut. Reduction or prevention of skin irritation or sensitization during transdermal administration of an irritating or sensitizing drug. US patent 5,451,407, 1995.
22. M Cormier, PW Ledger, A Amkraut. Reduction or prevention of skin irritation of drugs. US patent 5,130,139, 1992.
23. RV Padmanabhan, JB Phipps, GA Lattin, RJ Sawchuk. In vitro and in vivo evaluation of transdermal iontophoretic delivery of hydromorphone. J Control Rel 11:123–125, 1990.
24. R Gyory, JB Phipps, R Padmanabhan. Comparison of in vitro and in vivo iontophoretic transport rates of several therapeutic compounds. In: P Couvreur, D Duchene, P Green, HE Junginger, eds. Transdermal Administration, a Case Study, Iontophoresis. APGI/CRS European Symposium. Paris: Editions de Sante, 1997, pp. 351–354.
25. SK Gupta, KJ Bernstein, H Noorduin, A Van Peer, G Sathyan, R Haak. Fentanyl delivery from an electrotransport system: delivery is a function of total current, not duration of current. J Clin Pharmacol 38:951–958, 1998.
26. SK Gupta, MA Southam, G Sathyan, M Klausner. Effect of current density on pharmacokinetics following continuous or intermittent input from a fentanyl electrotransport system. J Pharm Sci 87:976–981, 1998.
27. SK Gupta, G Sathyan, B Phipps, M Klausner, M Southam. Reproducible fentanyl doses delivered intermittently at different time intervals from an electrotransport system. J Pharm Sci 88:835–841, 1991.
28. JE Moodie, CR Brown, SF Jones, EI Bisley. Efficacy and safety of Transfenta, a transdermal electrotransport delivery system, for the management of postoperative pain following short-stay surgical procedures. Am Pain Soc, San Diego, CA, 1998 (abstract).
29. MB Delgado-Charro, RH Guy. Iontophoretic delivery of Nafarelin across the skin. Int J Pharm 117:165–172, 1995.

Copyright © 2003 Marcel Dekker, Inc.

42

Microfabricated Microneedles for Transdermal Drug Delivery

Mark R. Prausnitz
Georgia Institute of Technology, Atlanta, Georgia, U.S.A.

Donald E. Ackley* and J. Richard Gyory†
Redeon, Inc., Burlington, Massachusetts, U.S.A.

I. INTRODUCTION

Drug delivery technologies strive to balance the ability to deliver drugs effectively with the ability to do so in a patient-friendly manner [1,2]. Injection or infusion through a hypodermic needle is the gold standard for effective delivery, since large amounts of drug of any size can be administered with controlled kinetics. However, the pain and inconvenience of needles have motivated alternative drug delivery approaches, such as transdermal drug delivery. By transporting drug across the skin either by passive diffusion or combined with chemical, electrical, ultrasonic, or other enhancers, transdermal delivery provides controlled release of drugs from a patient-friendly patch [3,4]. However, this approach is severely limited, because the skin's great barrier properties prevent most drugs from crossing skin at therapeutic rates.

To achieve a better balance between efficacy and convenience, we and others have proposed a hybrid of the hypodermic needle and transdermal patch through the use of microscopic needles that can deliver drugs effectively (like a hypodermic needle) and, because their small size makes them painless, are well tolerated by patients (like a transdermal patch) [5]. Although this idea received attention already in the 1970s [6], the technology needed to make microneedles became available only recently.

---

* *Current affiliation*: VSK Photonics, Irvine, California, U.S.A.
† *Current affiliation*: Transform Pharmaceuticals, Inc., Waltham, Massachusetts, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

The microneedle concept employs an array of micron-scale needles that is inserted into the skin sufficiently far that it can deliver drug into the body, but not so far that it hits nerves and thereby avoids causing pain. An array of microneedles measuring tens to hundreds of microns in length should be long enough to deliver drug into the epidermis and dermis, which ultimately leads to uptake by capillaries for systemic delivery [3,4]. When microneedle arrays are inserted into the skin, they can create conduits for transport across the stratum corneum, the outer layer of skin that forms the primary barrier to transport. Once a compound crosses the stratum corneum it can diffuse rapidly through deeper tissue and be taken up by the underlying capillaries. This is similar to conventional transdermal patch delivery, except the rate-limiting barrier of the stratum corneum is circumvented by the pathways created by microneedles.

Small microneedles can also be painless if designed with an understanding of skin anatomy. Human skin is made of three layers: stratum corneum, viable epidermis, and dermis [7]. The outer 10–15 μm of skin, called stratum corneum, is a dead tissue that forms the primary barrier to drug transport. Below lies the viable epidermis (50–100 μm), a tissue containing living cells and nerves, but no blood vessels. Deeper still, dermis forms the bulk of skin volume and contains living cells, nerves, and blood vessels. Therefore, microneedles that penetrate skin slightly more than 10–15 μm deep should provide transport pathways across the stratum corneum, but do so painlessly since microneedles do not reach nerves found in deeper tissue. Moreover, if microneedles do penetrate deeper into the skin, their odds of hitting a nerve should be reduced owing to their small diameter.

Needles of micron dimensions can be made using microfabrication technology, which is the same technology used to make integrated circuits [8]. In this microfabrication approach, silicon, metal, polymer, or other materials are exposed to masking steps, which define the shape of structures to be created, and chemical etching steps, which sculpt the material into the prescribed shapes. An advantage of this approach is that microfabrication readily makes structures of micron dimensions in a way that is easily scaled up for cheap and reproducible mass production.

II. FABRICATION OF MICRONEEDLES

To test the hypothesis that very small needles could increase skin permeability in a painless manner, we first fabricated solid, silicon microneedles. Silicon was employed because it is the most commonly used material in the microelectronics industry and solid needles were made because their fabrication was simpler than hollow ones. Subsequently, we made needles out of other materials—notably metal—and then developed techniques to make microneedles that are hollow.

Copyright © 2003 Marcel Dekker, Inc.

A. Microfabrication of Solid Silicon Microneedles

As a first prototype, we made small arrays of microneedles using a novel deep plasma etching technique based on the black silicon method [9]. Performed in a microelectronics cleanroom, this technique involves first depositing onto a silicon wafer a chromium mask, which defines the location and size of the microneedles. Then, in a reactive ion etcher, the silicon is chemically etched away preferentially at locations not covered by the mask. By adjusting the ratio of the SF_6 to O_2 in the etching plasma, the amount of "underetch" (i.e., etching underneath the protective mask) can be manipulated and thereby the needles' aspect ratio and sharpness can be controlled. The technique creates arrays of microneedles such as those shown in Figure 1, b and c.

These microneedles have two important structural features. First, they have extremely sharp tips (radius of curvature < 1 μm) that facilitate easy piercing into the skin. Second, they are approximately 150 μm long. Because the skin surface is not flat due to hair and dermatoglyphics (i.e., tiny wrinkles), the full length of these microneedles will not penetrate the skin. That which does penetrate should insert deep enough to cross the stratum corneum barrier but not so deep to hit nerves found in deeper tissue. The fabrication technique can easily be modified to make longer or shorter needles if needed.

These microneedles are orders of magnitude smaller than conventional needles. To illustrate this point, Figure 1a shows a conventional 26-gauge hypodermic needle and Figure 1b shows an array of microneedles at the same magnification.

B. Microneedles Made from Other Materials

Because silicon is the most common material used for microfabrication techniques, it was the material our first studies used. However, we prefer to use other materials, such as metals, which are stronger and have a record for safe use in humans. To demonstrate the feasibility of making microneedles from other materials, we made a mold of silicon microneedles and then filled the mold with metal (NiFe) by electroplating. The mold was made of polymeric photoresist (SU-8) and provided the inverse structure of the needles. Comparing the original silicon needles to the metal needles created with the mold showed that the metal needles were essentially identical replicas (data not shown). We have also employed a similar approach involving a mold to make microneedles out of polymers.

C. Microfabrication of Hollow Microneedles

There may be some advantages to delivering drugs through hollow microneedles, rather than solid ones. To make hollow microneedles, we electroplated a thin

Copyright © 2003 Marcel Dekker, Inc.

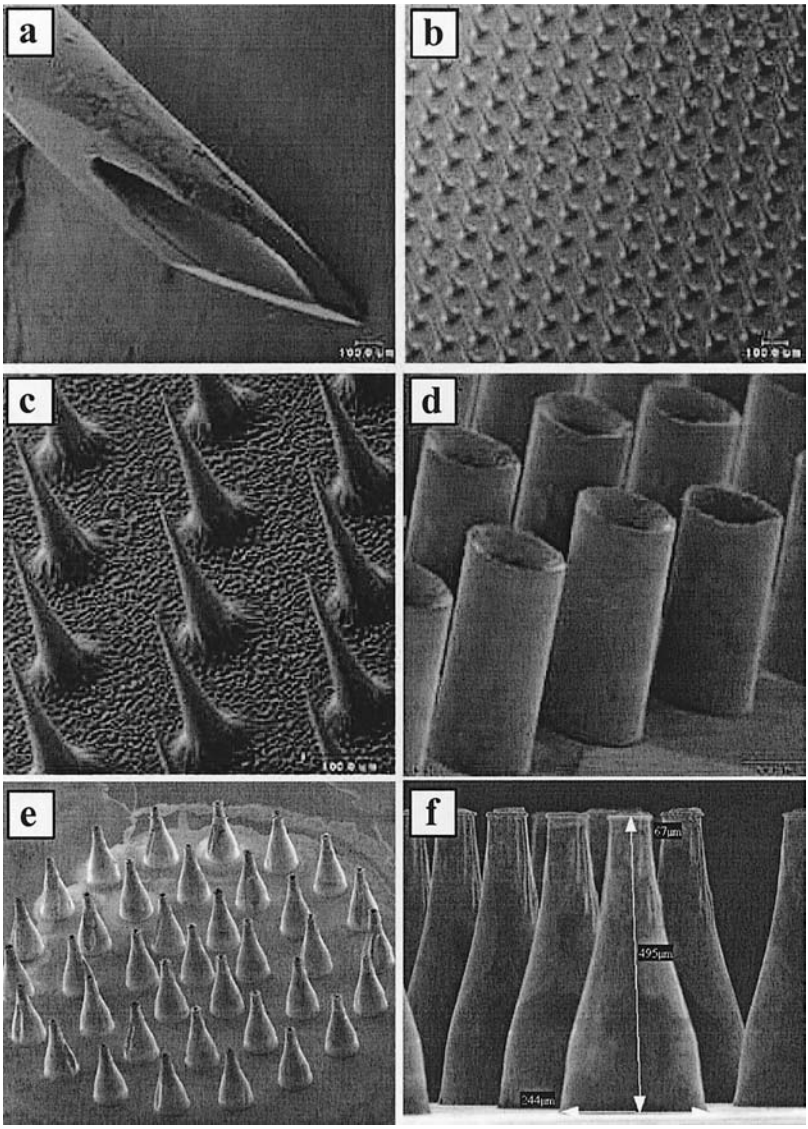


Figure 1 Scanning electron microscopy images of microneedles. (a) The tip of a conventional 26-gauge hypodermic needle is shown at the same magnification as (b) a portion of an array of microneedles. Images at greater magnification show (c) solid silicon microneedles (~150 μm tall) and (d) hollow metal microtubes (~150 μm tall). An array of somewhat larger microneedles (~500 μm tall) is shown at (e) lesser and (f) greater magnification. Reproduced from Refs. [10, 12] with permission.

Copyright © 2003 Marcel Dekker, Inc.

coating of metal (NiFe) onto the inner surface of molds similar to those made for solid metal needles, which left a thin metal shell in the shape of a needle [10], as shown in Figure 1, d–f. Testing of these prototype hollow needles indicated that they are mechanically strong enough to pierce skin and permit the passage of fluids, as described below.

III. TESTING OF MICRONEEDLES

One of the most important potential advantages of microneedles is the prospect that they can deliver drugs without the pain typically associated with conventional hypodermic needles. To test this possibility, we inserted arrays of 400 solid silicon microneedles (Fig. 1c) into the forearms of human volunteers [11]. The microneedles could be easily inserted into the skin (data not shown). Moreover, insertion of microneedle arrays was never reported as painful (Fig. 2). Sensation caused by microneedles was statistically indistinguishable from pressing a

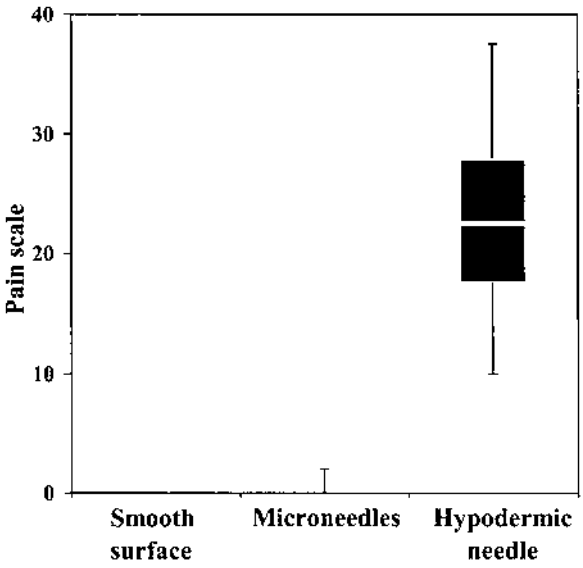


Figure 2 Box plot showing visual analog pain scores from a blinded comparison between (i) a smooth silicon surface, (ii) a 400-microneedle array (Fig. 1c) and (iii) a 26-gauge hypodermic needle (Fig. 1a) inserted into the forearm of human subjects. For each treatment, the fifth, twenty-fifth, fiftieth, seventy-fifth, and ninety-fifth percentiles are shown. Microneedles were reported as being painless. (Reproduced from Ref. [11] with permission.)

Copyright © 2003 Marcel Dekker, Inc.

smooth surface against the skin. In contrast, pain caused by a hypodermic needle was substantially greater than pain from microneedles. The skin into which microneedles had been inserted was visually inspected after the study. No redness or swelling was observed, suggesting that the microneedles had not caused damage or irritation. None of the subjects reported adverse reactions.

Another potential advantage of using microneedles is the ability to deliver large molecules across the stratum corneum. In vitro experiments using human cadaver epidermis mounted in standard diffusion chambers showed significant enhancement in rates of transdermal transport for a broad range of compounds. For example, calcein is a small, hydrophilic molecule (623 Da) representative in size of many conventional drugs. Without microneedles, skin permeability to calcein was undetectable, whereas insertion of microneedles into skin increased skin permeability by more than 3 orders of magnitude above the detection limit (Fig. 3) [9]. Insertion and subsequent removal increased skin permeability by more than 4 orders of magnitude.

Similar results were observed for transdermal delivery of insulin (6 kDa) and bovine serum albumin (66 kDa) (Fig. 3) [12]. Transport of polymeric nanoparticles was also observed at significant rates through skin permeabilized by needles inserted and then removed. Such large permeabilities to insulin, BSA, and nanospheres is remarkable, since until recently the skin was considered impermeable to macromolecules.

A similar in vitro experiment was performed to mimic extraction of molecules of interest from the skin. In this case, calcein solution was placed on the opposite side of the skin from the microneedle arrays in the same diffusion cell configuration described above. Similar increases in skin permeability were observed for the "extraction" of calcein as for its delivery (data not shown). These results could be important for minimally invasive methods of interstitial fluid sampling of interest for glucose monitoring of diabetics and other applications.

Hollow microneedles offer the opportunity to diffuse drug molecules or even flow drug solutions through needle bores. To demonstrate this possibility, we measured the flow rate of water though a 100-microneedle array as a function of pressure (Fig. 4). Flow rates of tens of milliliters per minute were measured at pressures of just a few psi, which are comparable to flow rates and pressures applied by hand to hypodermic needles attached to syringes.

IV. REGULATORY ISSUES

Microneedles used for drug delivery will be subject to approval by the U.S. Food and Drug Administration and its counterpart organizations in other countries. Specific registration issues for a particular microneedle product will depend partly

Copyright © 2003 Marcel Dekker, Inc.

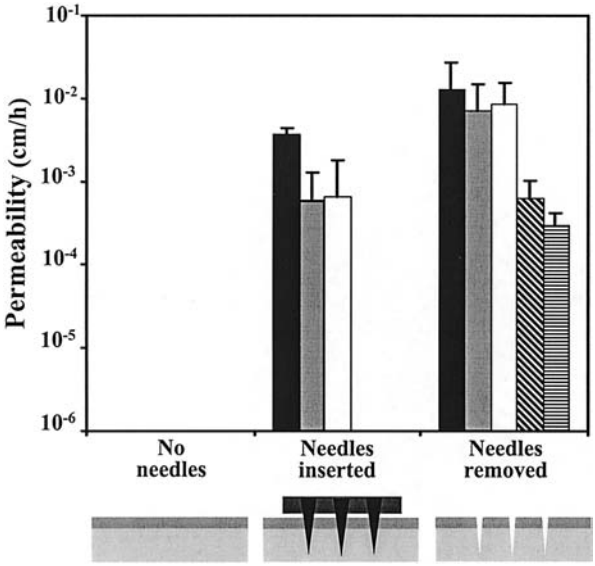


Figure 3 Skin permeability to calcein (black), insulin (gray), bovine serum albumin (white), 50-nm nanospheres (diagonal stripes), and 100-nm nanospheres (horizontal stripes) in vitro. Permeability is shown for intact skin (always below detection limit), skin with an array of 400 solid microneedles (Fig. 1c) inserted and left in the skin, and skin with an array of 400 solid microneedles inserted and then removed from the skin. Small molecules, proteins, and even nanospheres can be transported across skin using microneedles.

on properties of the microneedle device, but probably to an even greater extent on the nature of the compound, its therapeutic category and whether it is administered via a rapid single-use injection or a slow, long-term infusion. Because no drug to date has been directly delivered to the superficial layers of skin for systemic uptake, regulatory bodies may view microneedles as a new route of delivery. However, the transport route employed by microneedle-assisted delivery and conventional transdermal patch delivery have some similarities.

Both safety and efficacy studies will be expected for registration of a microneedle product and even the use of microneedles as a general injection device will have to be studied and possibly approved on a drug-by-drug basis. Particular attention needs to be paid to possible sensitization responses to drug or formulation excipients administered into skin using microneedles. Because microneedles breach the stratum corneum barrier, a sterile and pyrogen-free device and formulation may be required.

Copyright © 2003 Marcel Dekker, Inc.

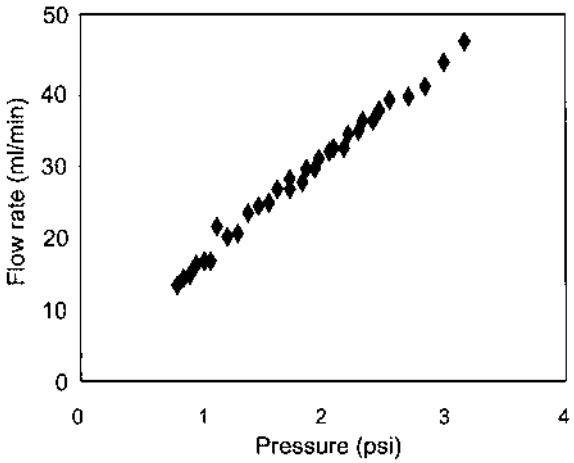


Figure 4 Flow rate of water through an array of 100 hollow microtubes (Fig. 1d) as a function of pressure. Very small pressures, e.g., a few psi, are sufficient to flow water through arrays of microneedles at rates of many milliliters per minute.

V. TECHNOLOGY POSITION AND FUTURE DIRECTIONS

A. Comparison with Hypodermic Needles and Transdermal Patches

Microneedles have many of the advantages of both conventional needles and transdermal patches. Capturing the effectiveness of hypodermic needles, microneedles create transport pathways sufficiently large to deliver small drugs, macromolecules, and even drug-loaded nanoparticles into and across the skin. Capturing the user-friendliness of transdermal patches, microneedles are short and thin, which means they should be painless and can be incorporated into a small, wearable device.

The drugs that can be delivered using microneedles may have many of the restrictions imposed by hypodermic needles and transdermal patches. For example, highly irritating formulations generally cannot be injected subcutaneously or intramuscularly and probably cannot be administered using microneedles either. Also, transdermal formulations administered at high concentrations within skin can stimulate sensitization reactions to drugs and excipients. Because microneedles deposit drug formulations near the epidermis-dermis junction, where immune-responsive cells reside [7], it is likely that the microneedle delivery route will also be limited to nonimmunoreactive compounds and formulations. How-

Copyright © 2003 Marcel Dekker, Inc.

ever, this limitation may present an opportunity for delivery of vaccines [13], which may elicit improved immune responses when administered with microneedles. Moreover, some dermatological applications [7] and gene therapy applications [14] may also benefit from having direct access to the epidermis-dermis juncture.

B. Microneedle Application Scenarios

Microneedle arrays could be used for short-term delivery in a manner similar to conventional injection. The advantage of microneedles is that they could provide that injection painlessly. However, this may not be the area in which microneedles have the most impact. It is unlikely that microneedles will be able to rapidly deliver large volumes of drug solution into the spatially confined skin. Moreover, direct access to the bloodstream is difficult with microneedles, making rapid infusion problematic. However, for those applications where smaller volumes can be delivered over longer periods of time (i.e., more than a few seconds) and the pain-free and other advantages of microneedles are important, short-term delivery with microneedles should be an attractive method.

Drug delivery over hours to days is where microneedles have the potential to make the greatest impact. By adding microneedles to a device similar to current transdermal patches, large and hydrophillic drugs like insulin or heparin could be delivered continuously across the skin in the same way that small, hydrophobic drugs like nicotine are currently administered from patches. When coupled with additional driving forces using a pump or iontophoresis, delivery rates could be increased and even modulated according to a preprogrammed schedule or in response to input from the patient or health care worker.

In addition to drug delivery for therapeutic purposes, microneedles may also be useful for pain-free extraction of interstitial fluid for diagnostic purposes. For example, it has already been demonstrated that the glucose content of interstitial fluid can be correlated to systemic glucose levels [15]. Thus, if microneedles can be used to extract interstitial fluid, they can be an important tool for the diagnostic industry for measurement of solutes.

ACKNOWLEDGMENTS

This work was supported in part by the National Institutes of Health, National Science Foundation, and American Diabetes Association. We thank Mark Allen, Shawn Davis, Inder-Jeet Gujral, Sebastien Henry, Shilpa Kaushik, and Devin McAllister for providing experimental data and helpful discussions.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. R Langer. Drug delivery and targeting. Nature 392:5–10, 1998.
2. K Park. Controlled Drug Delivery: Challenges and Strategies. Washington, DC: American Chemical Society, 1997.
3. MR Prausnitz. Reversible skin permeabilization for transdermal delivery of macromolecules. Crit Rev Ther Drug Carr Syst 14:455–483, 1997.
4. EW Smith, HI Maibach. Percutaneous Penetration Enhancers. Boca Raton, FL: CRC Press, 1995.
5. DV McAllister, MG Allen, MR Prausnitz. Microfabricated microneedles for gene and drug delivery. Annu Rev Biomed Eng 2:289–313, 2000.
6. MS Gerstel, VA Place. Drug delivery device. US patent 3,964,482, 1976.
7. RH Champion, JL Burton, FJG Ebling. Textbook of Dermatology. London: Blackwell Scientific, 1992.
8. WR Runyan, KE Bean. Semiconductor Integrated Circuit Processing Technology. New York: Addison-Wesley, 1990.
9. S Henry, DV McAllister, MG Allen, MR Prausnitz. Microfabricated microneedles: a novel method to increase transdermal drug delivery. J Pharm Sci 87:922–925, 1998.
10. DV McAllister, F Cros, SP Davis, LM Latta, MR Prausnitz, MG Allen. Three-dimensional hollow microneedle and microtube arrays. Proc Transduc 99:1098–1101, 1999.
11. S Kaushik, AH Hord, DD Denson, DV McAllister, S Smitra, MG Allen, MR Prausnitz. Lack of pain associated with microfabricated microneedles. Anesth Analg 92: 502–504, 2001.
12. D McAllister, S Kaushik, P Patel, J Mayberry, M Allen, M Prausnitz. Solid and hollow microneedles for transdermal protein delivery. Proc Int Symp Control Rel Bioact Mater 26:192–193, 1999.
13. MF Powell. Drug delivery issues in vaccine development. Pharm Res 13:1777–1785, 1996.
14. JA Wolff. Gene Therapeutics: Methods and Applications of Direct Gene Transfer. Boston: Birkhäuser, 1994.
15. J Tamada, S Garg, L Jovanovic, K Pitzer, S Fermi, R Potts. Noninvasive glucose monitoring: comprehensive clinical results. Cygnus Research Team. JAMA 282: 1839–1844, 1999.

Copyright © 2003 Marcel Dekker, Inc.

43

Metered-Dose Transdermal Spray (MDTS)

Timothy M. Morgan
Acrux Limited, Melbourne, Victoria, Australia

Barry L. Reed and Barrie C. Finnin
Monash University (Parkville Campus), Parkville, Victoria, Australia

I. INTRODUCTION

The growth of specialty pharmaceuticals in the marketplace continues to provide the impetus to further explore the practical application of basic pharmaceutical research. New drug products utilizing oral controlled-release, inhalation, implant, and transdermal delivery systems will be responsible for driving the growth of this sector into the next decade [1].

Current transdermal drug delivery (TDD) technology relies chiefly upon occlusive patches, and this dosage form is now considered to be a mature technology [1]. A new metered-dose transdermal spray (MDTS™), originally developed at the Victorian College of Pharmacy (Monash University) and currently being commercialized by Acrux Limited, has the potential to expand the current annual double-digit growth of TTD systems by broadening patient acceptance and pharmaceutical applications for enhanced TDD.

The MDTS relies on the combination of newly identified GRAS (generally recognized as safe) chemical penetration enhancers (Across™) and the accurate and precise topical dosing of a volatile:nonvolatile vehicle. This MDTS can be classified as an enhanced, passive TDD system, and to date it has shown promising results during initial feasibility studies [2] that involved in vitro [3], in vivo pig [4], and pilot human studies [5].

A foundation for the regulatory development of the MDTS for existing drugs lies in the utilization of comparative bioequivalence as a major regulatory pathway to facilitate marketing approval. Once-daily administration of an estradiol MDTS to postmenopausal women has been demonstrated to provide similar

Copyright © 2003 Marcel Dekker, Inc.

average serum concentrations of estradiol compared to the Estraderm® 50 patch, without the problem of application site irritation often seen with transdermal patches.

The market potential exists to establish a strong competitive position using the once-daily MDTS for TDD, which would offer the advantages of lower skin irritation, greater ease of use, increased dosage flexibility, and a simple manufacturing method.

II. HISTORICAL DEVELOPMENT

The need to improve the bioavailability of percutaneous drug delivery systems has driven an exhaustive search for new skin penetration enhancers [6]. While chemical penetration enhancers such as laurocapram (Azone®) have shown good overall enhancing abilities [7,8], they have failed to gain general clinical acceptance because of their potential to irritate the skin [9–12]. Consequently, much of our research has focused on the discovery of penetration enhancers that are GRAS, and yet still maintain enhancing abilities as good as, or superior to, those of laurocapram. The need for an improved passive TDD platform has also been a significant research focus.

III. MDTS

The MDTS is a topical solution made up of a volatile:nonvolatile vehicle containing the drug dissolved as a single-phase solution. A finite metered-dose application of the formulation to intact skin results in subsequent evaporation of the volatile component of the vehicle, leaving the remaining nonvolatile penetration enhancer and drug to rapidly partition into the stratum corneum during the first minute after application, resulting in a stratum corneum reservoir of drug and enhancer [3], as diagramatically represented in Figure 1.

Following a once-daily application of the MDTS a sustained and enhanced penetration of the drug across the skin can be achieved from the stratum corneum reservoir [3,4].

A. Possible Enhancement Mechanisms

While ethanol can act as a penetration enhancer, and various mechanisms of action have been postulated [13], in practice its use as a penetration enhancer has relied upon the application of a bulk aqueous ethanol vehicle to the skin where the increase in the flux of the drug across the skin is mainly due to a solvent drag effect as previously described [14]. The ethanol in the MDTS is unlikely

Copyright © 2003 Marcel Dekker, Inc.

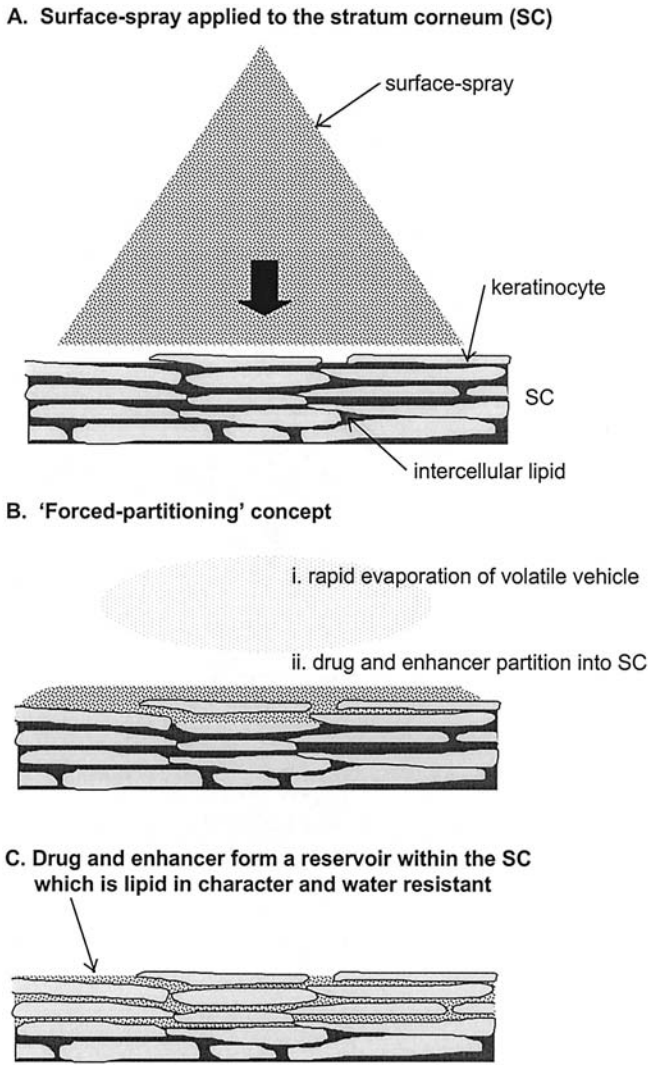

A. Surface-spray applied to the stratum corneum (SC)
surface-spray
keratinocyte
SC
intercellular lipid
B. 'Forced-partitioning' concept
i. rapid evaporation of volatile vehicle
ii. drug and enhancer partition into SC
C. Drug and enhancer form a reservoir within the SC
which is lipid in character and water resistant

Figure 1 Schematic representation of the partitioning process for a rapid-drying, topical spray formulation [2].

Copyright © 2003 Marcel Dekker, Inc.

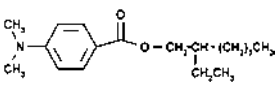
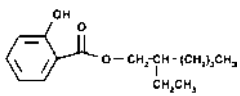
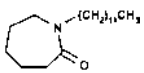
to act as a penetration enhancer because at the volumes applied (<4 μL/cm^2) the ethanol is merely acting as an intermediary solvent to spread the drug and enhancer over the skin.

Like Azone [15], the Across enhancers have been shown to lower the transition temperature of stratum corneum lipids [16], which is postulated to result in significant increases in drug diffusivity across the skin. Whether potential increases in drug diffusivity are related primarily to stratum corneum lipid fluidization or lipid phase separation, as proposed for oleic acid [17], remains to be determined. The stratum corneum is the likely target site of the Across enhancers as they have a high affinity for this region because of their large log P values (see next section), and their solubility parameters are similar to the stratum corneum. The stratum corneum has an estimated solubility parameter between 19.8 and 20.5 Mpa$^{0.5}$ [18].

IV. RESEARCH AND DEVELOPMENT

A series of GRAS compounds that have traditionally been used as chemical sunscreens are the basis for the new Across penetration enhancers, which are exem-

Table 1 Structure, Physicochemical Properties, and Classification of Chemical Penetration Enhancers

Padimate O	Octyl salicylate	Laurocapram (Azone)
		
Mol. wt[a] = 277.4	250.3	281.5
Log P[b] = 5.77	5.97	6.28
Classification: inorg./org.[c] = $^{145}/_{330}$	$^{175}/_{290}$	$^{135}/_{360}$
Nonvolatile, pale-yellow, mobile liquid, characteristically mild odor; insoluble in water; freely soluble in absolute ethanol	Nonvolatile, colorless to pale-yellow liquid, characteristically bland odor; insoluble in water; freely soluble in absolute ethanol	Nonvolatile, colorless liquid, characteristically mild odor; insoluble in water; freely soluble in absolute ethanol

[a] Compound names, structure, mol. wt., physical form, and solubility taken from Martindale, The Extra Pharmacopoeia, 31st ed., London: The Pharmaceutical Press, 1997.

[b] log P = octanol:water partition coefficient taken from the log K_{ow} online database (Syracuse Research Corporation, Syracuse, NY).

[c] Calculated from data of Hori et al. [21].

Source: Adapted from Ref. [21].

Copyright © 2003 Marcel Dekker, Inc.

plified by octyl salicylate USP and padimate O USP [19]. Both have been extensively used as safe and effective sunscreens for over 20 years [20]. The physicochemical properties of two of the Across enhancers are shown in Table 1, with laurocapram (Azone) included for comparison.

The comparative enhancement effects of octyl salicylate (OSal), padimate O (PadO), and Azone (AZ) on testosterone skin penetration following a single application of a MDTS vehicle are shown in Figure 2.

Similar enhancement effects have been observed in vitro for other sex hormones [3], and in vivo studies in domestic weanling pigs have shown a twofold and 14-fold increase in AUC_{0-24h} following once-daily application of a testosterone and estradiol MDTS (aerosol version), respectively [4].

Clinical experience with the estradiol MDTS began with a pilot pharmacokinetic study in postmenopausal women [5]. The estradiol MDTS (aerosol version, with PadO) was applied once daily at 0800 h to postmenopausal women for 9 days and plasma estradiol and estrone levels were measured daily (24 h postapplication) by radioimmunoassay. The topical dose was administered as

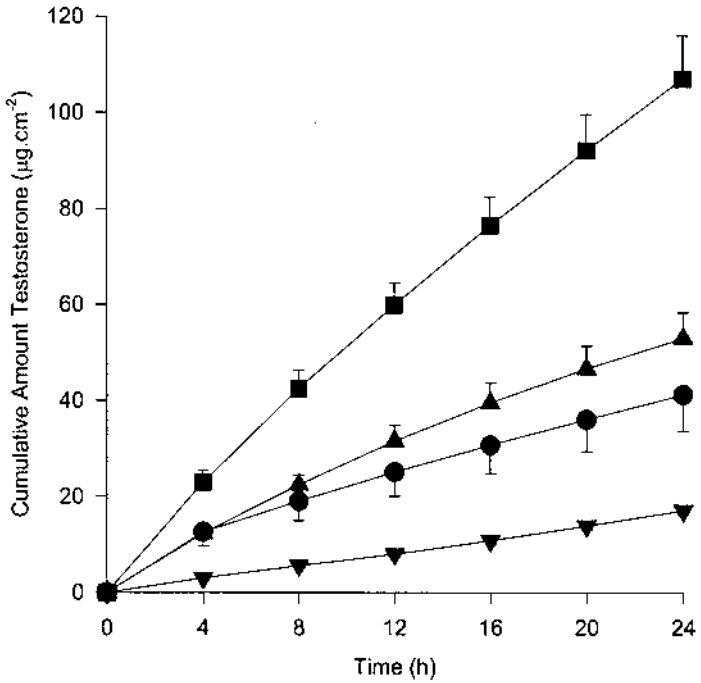


Figure 2 The effect of octyl salicylate (■), Azone (▲), and padimate O (●) on the diffusion of testosterone across Children's python snake skin in vitro (mean ± SE, n = 4) compared with control (▼). (Adapted from Ref. [3].)

Copyright © 2003 Marcel Dekker, Inc.

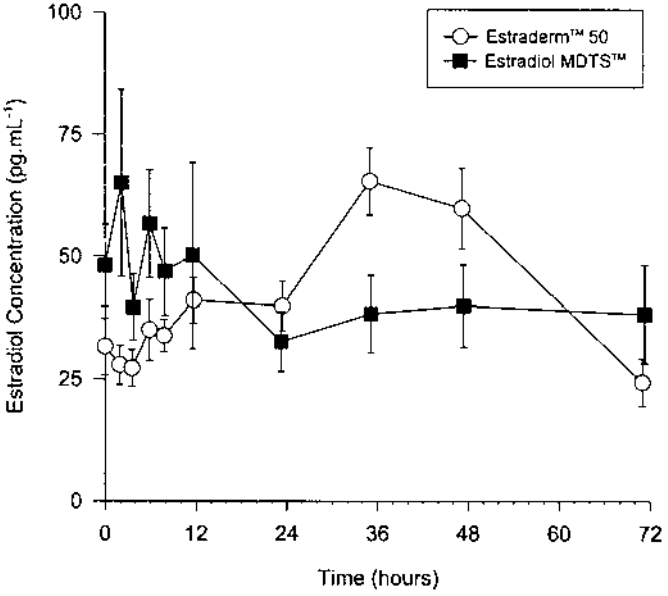


Figure 3 Mean (±SE, $n = 8$) serum estradiol concentrations after administration of Estraderm 50 patch (3.5-day dose) and estradiol MDTS (once-daily dose) to healthy postmenopausal women. Both treatments were applied for 6 days, with the pharmacokinetic comparison performed over 72 h, during days 4–7. (Courtesy of A. Humberstone, Acrux Limited, Parkville, Victoria, Australia, unpublished data.)

three 1-mg doses of estradiol, each applied as a single spray over 10 cm^2, which were placed adjacent to each other on each subject's ventral forearm. None of the subjects tested showed any sign of skin irritation at the application site over the entire study period as assessed by the Draize irritation score. In four postmenopausal women (age: 54–63 years, weight: 67–93 kg) the mean estradiol level 24 h postapplication over the 9-day study period was 53 pg/mL. This result was significantly greater ($p < 0.001$) than the baseline value of 13 pg/mL. The mean estradiol/estrone ratio also rose significantly ($p < 0.04$) from a baseline value of 0.2 up to 0.8.

More recently, a pilot comparative bioequivalence study conducted with healthy postmenopausal women compared the Estraderm® patch (0.05 mg/day) and an estradiol MDTS (with OSal). The steady-state results, shown in Figure 3, demonstrate the ability of this new TDD system to provide estradiol levels that are comparable to those observed for the Estraderm patch (0.05 mg/day).

Copyright © 2003 Marcel Dekker, Inc.

V. REGULATORY ISSUES

The functionality or performance of the MDTS can be considered from a regulatory standpoint as a container closure that is both a metered-dose topical solution and a transdermal system. The design of appropriate stability tests then becomes a relatively straightforward task given the advent of modern regulatory agency guidance [22].

A feature associated with nonocclusive transdermal systems, such as the MDTS, is the need to test for adhesion (substantivity on and within the skin). Specifically, nonocclusive transdermal systems raise the possibility of patient-to-partner transfer and/or changes in percutaneous bioavailability following bathing. The former issue has been reported for a testosterone ointment used by a male patient, which led to virilization in his female sexual partner [23]. Suitable in vitro [3] and in vivo [4] "effect-of-washing studies" have been developed to monitor these potentially problematic formulation issues.

Another point of difference is that a transdermal release rate test for a MDTS should not be necessary, given the previous consensus opinion of a group of regulatory and transdermal leaders [24]. In reference to the need for a transdermal release rate test, the authors state, "In those few instances when the topical dosage forms involve total solution of a drug in a well-characterized solvent system, data showing that the concentration of the drug is invariant from batch-to-batch is considered adequate" [24].

VI. COMPETITIVE ADVANTAGES OF THE MDTS

TDD remains one of the "big four" DDS in terms of market value, and is projected to remain so over the next decade even it if continues to be based around patch technology. Recent innovations in patch design and manufacture have produced only incremental improvements (e.g., thinner patch, clear patch) [25] rather than solving the major problems of skin irritation [25,26] and the complexity of manufacture [27].

The MDTS has the potential to offer enhanced passive TDD with little or no skin irritation primarily as a result of its nonocclusive nature and the skin tolerability of the Across enhancers. Improved cosmetic acceptability compared to patches, gels, and creams has been achieved through the judicious use of excipients in what amounts to a no-touch, microdose formulation that maintains good enhancement capability at low doses of the Across enhancers.

The inherent dosage flexibility of the MDTS and the simplicity of manufacture provide a significant cost-of-goods advantage relative to traditional transdermal systems.

The combined advantages of TDD itself [5] and those of the MDTS out-

Copyright © 2003 Marcel Dekker, Inc.

lined above create a potential new DDS offering what will, hopefully, one day benefit each of the "three P's" of modern health care: patients, physicians, and payers.

VII. FUTURE DIRECTIONS

As pharmaceutical applications are found for the MDTS, and it becomes an accepted DDS, it is anticipated that the experience base with the Across enhancers will expand into areas such as topical, transmucosal, and veterinary applications.

REFERENCES

1. AS Forman, DS Moskowitz. Rising to Another Level. Speciality Pharmaceuticals. New York: UBS Warburg LLC, 2000.
2. TM Morgan. Transdermal drug delivery with topical aerosols. PhD dissertation. Victorian College of Pharmacy (Monash University), Parkville, Victoria, Australia, 1998.
3. TM Morgan, BL Reed, BC Finnin. Enhanced skin permeation of sex hormones with novel topical spray vehicles. J Pharm Sci 87:1213–1218, 1998.
4. TM Morgan, RA Parr, BL Reed, BC Finnin. Enhanced transdermal delivery of sex hormones in swine with a novel topical aerosol. J Pharm Sci 87:1219–1225, 1998.
5. TM Morgan, HMM O'Sullivan, BL Reed, BC Finnin. Transdermal delivery of estradiol in postmenopausal women with a novel topical aerosol. J Pharm Sci 87:1226–1228, 1998.
6. BC Finnin, TM Morgan. Transdermal penetration enhancers: applications, limitations, and potential. J Pharm Sci 88:955–958, 1999.
7. RB Stoughton. Enhanced percutaneous absorption with 1-dodecylazacycloheptan-2-one (Azone). Arch Dermatol 118:474–477, 1982.
8. R Vaidyanathan, VJ Rajadhyaksha, BK Kim, JJ Anisko. Azone. In: AF Kyodenius, B Berner, eds. Transdermal Delivery of Drugs. Vol. 2. Boca Raton, FL: CRC Press, 1987, pp. 63–83.
9. H Okamoto, M Hasida, H Sezaki. Structure-activity relationship of 1-alkyl- or 1-alkenylazacycloalkanone derivatives as percutaneous penetration enhancers. J Pharm Sci 77:418–424, 1988.
10. UT Lashmar, J Hadgraft, N Thomas. Topical application of penetration enhancers to the skin of nude mice: a histopathological study. J Pharm Pharmacol 41:118–122, 1989.
11. O Wong, J Huntington, T Nishihata, JH Rytting. New alkyl *N*,*N*-dialkyl-substituted amino acetates as transdermal penetration enhancers. Pharm Res 6:286–295, 1989.
12. H Okabe, Y Obata, K Takayama, T Nagai. Percutaneous absorption enhancing effect and skin irritation of monocyclic monoterpenes. Drug Des Del 6:229–238, 1990.

Copyright © 2003 Marcel Dekker, Inc.

13. E Manabe, K Sugibayashi, Y Morimoto. Analysis of skin penetration enhancing effect of drugs by ethanol-water mixed systems with hydrodynamic pore theory. Int J Pharm 129:211–221, 1996.
14. B Berner, GC Mazzenga, JH Otte, RJ Steffens, R Juang, CD Ebert. Ethanol:water mutually enhanced transdermal therapeutic system. II. Skin permeation of ethanol and nitroglycerin. J Pharm Sci 78:402–407, 1989.
15. BW Barry. Mode of action of penetration enhancers in human skin. J Control Rel 6:85–97, 1987.
16. EL White, BL Reed, BC Finnin. Effect of padimate O, octyl salicylate and laurocapram on the thermal profile of a model stratum corneum lipid mixture. Proceedings of the Australian Pharmaceutical Science Association Conference, Sydney, Australia, 1997, p. 45.
17. A Naik, LARM Pechtold, RO Potts, RH Guy. Mechanism of oleic acid–induced skin penetration enhancement in vivo in humans. J Control Rel 37:299–306, 1995.
18. Z Liron, S Cohen. Percutaneous absorption of alkanoic acids. II. Application of regular solution theory. J Pharm Sci 73:538–542, 1984.
19. BL Reed, TM Morgan, BC Finnin. Dermal penetration enhancers and drug delivery systems involving same. WO 9729735A1, 1997.
20. JO Funk, SH Dromgoole, HI Maibach. Sunscreen intolerance. Dermatol Clin 13: 473–481, 1995.
21. M Hori, S Satoh, HI Maibach. Classification of percutaneous penetration enhancers: a conceptual diagram. J Pharm Pharmacol 42:71–72, 1990.
22. Guidance for Industry (Final). Container Closure Systems for Packaging Human Drugs and Biologics. Rockville, MD: Food and Drug Administration, May 1999.
23. D Delanoe, B Fougeyrollas, L Meyer, P Thonneau. Androgenization of female partners of men on medroxyprogesterone acetate/percutaneous testosterone contraception. Lancet 1:276, 1984.
24. JP Skelly, VP Shah, HI Maibach, RH Guy, RC Wester, G Flynn, A Yacobi. FDA and AAPS Report of the Workshop on Principles and Practices of In Vitro Percutaneous Penetration Studies: relevance to bioavailability and bioequivalence. J Pharm Sci 4: 265–267, 1987.
25. 3M Drug Deliv News. Vol. 11, 1998.
26. D Ross, M Rees, V Godfree, A Cooper, D Hart, C Kingsland, M Whitehead. Randomised crossover comparison of skin irritation with two transdermal oestradiol patches. Br Med J 315:288, 1997.
27. GA Van Buskirk, MA Gonzalez, VP Shah, S Barnhardt, C Barrett, S Berge, G Cleary, K Chan, G Flynn, T Foster, R Gale, R Garrison, S Gochnour, A Gotto, S Govil, VA Gray, J Hammar, S Harder, C Hoiberg, A Hussain, C Karp, H Llanos, J Mantelle, P Noonan, D Swanson, H Zerbe. Scale-up of adhesive transdermal drug delivery systems. Pharm Res 14:848–852, 1997.

Copyright © 2003 Marcel Dekker, Inc.

44

Transfersomes: Innovative Transdermal Drug Carriers

Gregor Cevc
IDEA AG, Munich, Germany

I. INTRODUCTION

Adverse side effects, drug metabolism by first-pass effect in the liver, poor patient compliance, or rejection of an invasive medication often hampers the success and efficacy of therapeutic treatment. Many scientists have tried to overcome these hurdles by designing better and safer drug delivery strategies. In the early 1980s, liposomes were among the most promising drug carriers [1], with high hopes also being put in dendrimers [2] and other complex polymer systems.

Transport of drugs through the skin has been repeatedly considered, since the skin is the largest human organ, with a total weight of 3 kg and a surface of 1.5–2.0 m^2. However, the majority of drugs cannot permeate through the intact skin, which presents one of the best biological barriers, due to the structural, biochemical, and physiological properties of the organ (Fig. 1, left panel). Chemical skin permeation enhancers, iontophoresis, sonoporation, electroporation, and many other methods have been investigated to increase the efficacy of transdermal transport. Owing to their limited efficacy, resulting skin irritation, complexity of usage, and/or high cost, none of these methods have been broadly applied to date.

Lipid-based suspensions, such as liposomes, niosomes, or microemulsions, have also been proposed as low-risk drug carriers. The problem with such vehicles is that they remain mostly confined to the skin surface and therefore do not transport drugs efficiently through the skin. To date, the most promising transdermal drug carrier is the recently developed and patented Transfersome®, which penetrates the skin barrier along the transcutaneous moisture gradient. This leads

Copyright © 2003 Marcel Dekker, Inc.

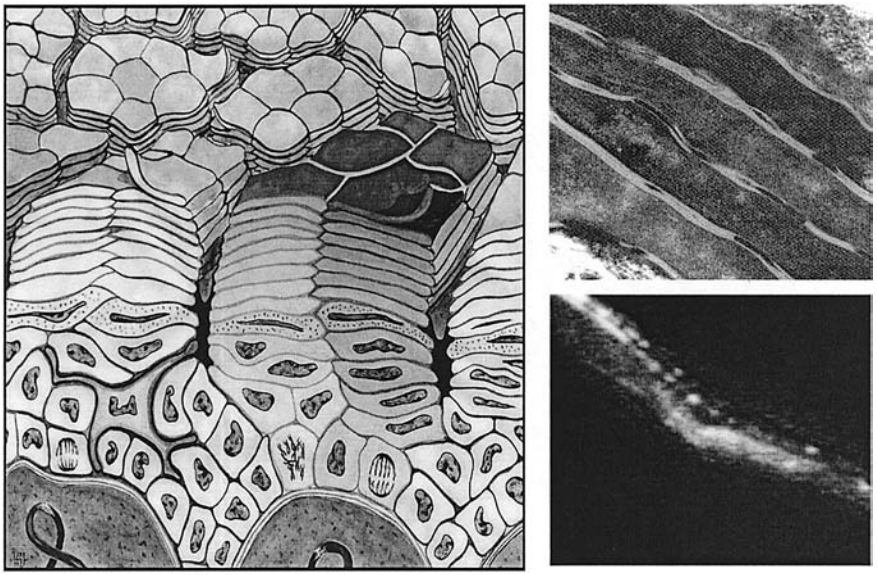


Figure 1 The skin (left panel) has an evolutionary optimized barrier, located mainly in the stratum corneum near the organ surface. This prevents material transport through this barrier, which is a combination of an anatomical barricade, consisting of cells arranged in a tile-like fashion, and a biochemical obstacle, in the form of tightly packed lipidic seals attached to the cells (dark bands in the upper right panel; electron micrograph). Possible routes through the skin pursue the path of lowest resistance between or along such hindrances (bright bands in the lower right panel; light micrograph). However, such "virtual channels" need first to be opened up to become effective. This requires application of special vehicles, such as Transfersomes, on the skin.

the carriers through the "virtual" pores between the cells in the organ without affecting its biological and general barrier properties (Fig. 1, right panels). Owing to this unusual barrier penetration mechanism, Transfersome carriers can create a highly concentrated drug depot in the skin [3], deliver material into deep subcutaneous tissue [4], or even deliver the drug into the systemic circulation [5]. A number of published patents describe how efficiently this is done [6–10].

II. HISTORICAL DEVELOPMENT

Although the skin is a naturally optimized barrier, it is an interesting target for noninvasive drug delivery into the body, for local as well as systemic treatment. Drug delivery through the skin (using transdermal therapeutic systems, TTS, or

Copyright © 2003 Marcel Dekker, Inc.

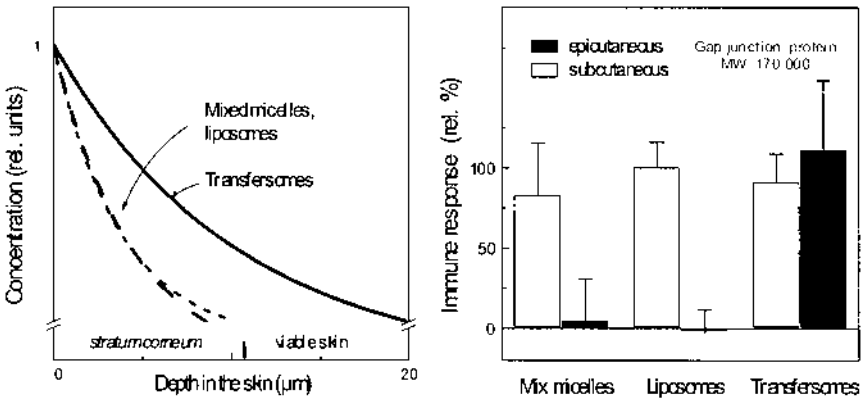


Figure 2 Specially designed, highly adaptable entities, such as Transfersomes, are needed to overcome the skin barrier, through virtual channels between the skin cells. This is reflected in the different skin penetration profiles and in the ability of Transfersomes to deliver large molecules, such as hexamers of gap junction protein (mol. wt. ~180 kDa) transcutaneously into the body.

transdermal delivery systems, TDS) was first introduced on the market in 1980. Since then, TTS/TDS in the form of patches have firmly established themselves in the pharmaceutical industry. However, the TDS market growth has been restricted by the limited range of drugs that can efficiently permeate the skin from patch formulations. Indeed, only some low-molecular-weight agents, such as nicotines, nitrates, estrogens, and androgens, and strong analgesics are sufficiently small and possess optimal physicochemical properties to permeate through the skin efficiently from a dermal patch. In the search to deliver drugs with unfavorable permeation characteristics or high-molecular-weight substances (such as insulin) through the skin, permeation enhancers, different skin perforation (poration) methods, and particulate carriers (liposomes, nanoparticles, etc.) have been tested. While the former two were efficient but poorly tolerated, the latter invariably failed to demonstrate significant skin penetration. Further development has shown that only specially designed, highly deformable lipid aggregates, so-called Transfersomes, can meet the expectations (Fig. 2) and can expand the range of drugs that can be delivered through the skin.

III. TECHNOLOGY

Modern carrier-mediated transdermal drug delivery started with the work of several investigators exploring liposomes [11–14] or niosomes [15] on the skin. The

Copyright © 2003 Marcel Dekker, Inc.

original liposomes were typically water-containing phospholipid vesicles comprising mainly phosphatidylcholine supplemented with cholesterol, which stabilizes lipid bilayers and prevents leakage and vesicle aggregation. More recently, liposomes prepared from the skin lipids were introduced. Niosomes have a similar morphology, but are made of nonionic surfactants, typically alkyl-polyoxyethylene ethers, mixed with cholesterol. A Transfersome can also be made from phosphatidylcholine in the form of vesicles, but typically contain at least one component that controllably destabilizes the lipid bilayers and thus makes the vesicle very deformable (Fig. 3). Additives useful for the purpose are bile salts, polysorbates, glycolipids, alkyl or acyl-polyethoxylenes, etc. Proper choice and balance of Transfersome components are the key to obtaining exceptionally deformable, but sufficiently stable, aggregates, which are both prerequisites for the success of skin penetration by a Transfersome.

The outermost skin layer, the stratum corneum, is nearly dry and consists of a little over a dozen flat and partly overlapping dead cells (corneocytes), organized in stacks with the intercellular space sealed with tightly packed lipids (Fig. 1, right upper panel). This special cellular organization makes the skin practically

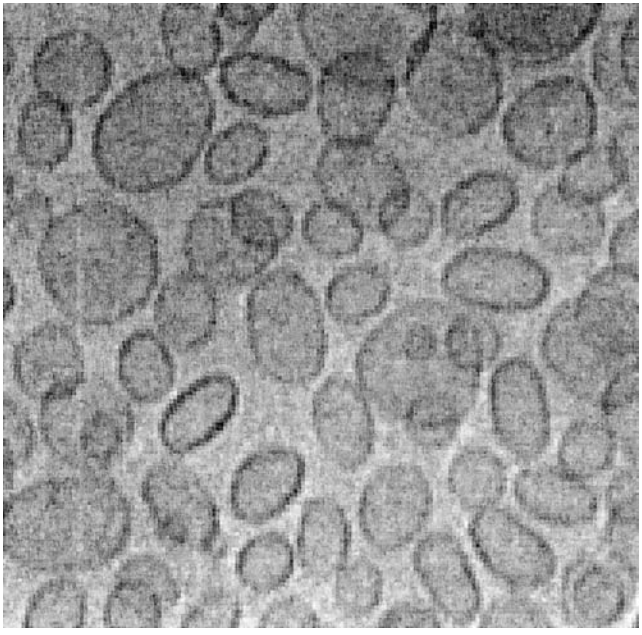


Figure 3 Transfersome vesicles, with highly flexible membranes, are sufficiently deformable to take a nonspherical form under the influence of thermal motion.

Copyright © 2003 Marcel Dekker, Inc.

impermeable, except to rare lipophilic compounds and to water vapor, which can cross the organ in a small quantity (<0.5 mg/h/cm^2). However, some intercellular regions are less tight than others. At places, where the lipidic seals are imperfect, tiny (<0.5 nm) hydrophilic pores exist through which water vapor evades the barrier (Fig. 1, lower right panel). Such pores can be opened into channels with a width of up to 20–30 nm [16] by applying unidirectional pressure on them. Nonocclusive administration of Transfersome suspension on the skin leads to the following effect: a Transfersome under stress of dehydration seeks to find water in the organ depth. This is only possible when the lipid aggregate enters the skin through a pore through which water molecules are streaming in the opposite direction. A typical Transfersome is 4–6 times bigger than an already opened channel. A carrier can therefore pass the potential pathways in the skin only if the effective Transfersome size, following vesicle deformation, becomes smaller than the channel width in at least one direction. High Transfersome membrane flexibility is one of the essential conditions for this process and this flexibility is not a characteristic of conventional liposomes or other commonly used vesicles [5].

Transfersome carriers loaded with various agents of different molecular size and lipophilicity (lidocaine, tetracaine, cyclosporin, diclofenac, tamoxifen, etc. [16,17]) have been shown to cross the skin barrier. In addition, polypeptides such as calcitonin, insulin, interferon-α and -γ, Cu-Zn superoxide dismutase [18], serum albumin, and dextran have been successfully delivered across the skin with Transfersome carriers [3,16].

Drug biodistribution following Transfersome-based transcutaneous delivery starts in the viable skin tissue. Small and soluble drugs leak out or dissociate from the carriers in this tissue and then diffuse into the blood. Larger released drugs or carriers, unable to enter the blood vessels, are either transported by intercellular fluid flow into the depth below the carrier application site or are taken through the fenestrations in lymph vessels into the lymphatic system and, finally, the systemic blood circulation. Sometimes, the first step is followed by the second, especially after local tissue gets saturated with the carrier and/or the drug. There are several reasons to believe that Transfersomes cross the skin intact and are taken up by the reticuloendothelial system, primarily in the liver [16].

IV. RESEARCH AND DEVELOPMENT

A. Transfersome Preparation

Transfersomes can be prepared easily using published and patented procedures [5,19]. Briefly, phosphatidylcholine (e.g., from soybean, SPC) is mixed, e.g., in ethanol, with sodium cholate or some other biocompatible surfactant. Subsequently, a suitable buffer is added to yield a total lipid concentration of approximately 10% by weight. The suspension is then sonicated, frozen, and thawed 2–

Copyright © 2003 Marcel Dekker, Inc.

3 times, to catalyze vesicle growth, and is finally brought to the preferred vesicle size by pressure homogenization, ultrasonication, or some other mechanical method. Final vesicle size, as determined with the dynamic light scattering, is approximately 120 nm for a typical Transfersome preparation containing 8.7% by weight SPC, 1.3% by weight sodium cholate, and up to 8.5% by volume ethanol. However, there is no general Transfersome formula or preparation protocol. The best carrier composition has to be found experimentally and for each drug separately to obtain appropriate Transfersome carriers with maximum deformability and stability [3].

B. Transfersome Characterization

The characterization of Transfersome and liposome suspensions has been performed both in vitro and in vivo.

An in vitro model has been developed that measures the relative ability of liposome and Transfersome vesicles to penetrate artificial barriers with passages resembling narrow channels in the skin. For this purpose, membrane filters with a known pore size between 30 nm and 400 nm are used, and the rate of pressure-driven vesicle suspension passage through the barrier is measured. This rate must be significantly (>10-fold) higher for Transfersomes than for liposomes (Fig. 4).

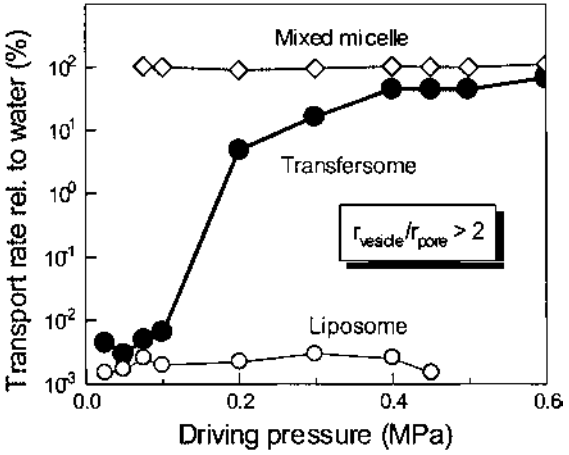


Figure 4 Transfersomes can cross a barrier with pores several times smaller than their own diameter, if stressed sufficiently, e.g., by an external, transport-driving pressure. In contrast, liposomes are confined to the application side, even under pressure, unless they are broken to a size smaller than the pore diameter. (From Ref. [14], with a minor adaptation.)

Copyright © 2003 Marcel Dekker, Inc.

Liposomes with a diameter larger than the pore size are typically retained by the filter. In contrast, a Transfersome passes the barrier even if its average size is four times larger than the pore size. Moreover, the constancy of aggregate size before and after the barrier passage is a sign of highly deformable vesicles and indicative of the ability of a Transfersome to cross the barrier without disintegration or fragmentation.

A further in vitro method has been developed for studying transdermal migration of Transfersome carriers that relies on skin biopsy punches or on vacuum-pulled skin blisters. Both are preferably done with skin from freshly slaughtered pigs. In brief, a dissected skin specimen, including connective tissue, is mounted on a cellulose sponge soaked with buffer, so that the stratum corneum faces the air and the subdermis is connected to the sponge. Suitably labeled Transfersome suspension is then applied to the tissue surface at ambient humidity and appropriate temperature without occlusion. For transport pathway characterization residual lipid suspension is eliminated from the skin surface with a dry cotton swab and subcutaneous adipose and connective tissue is removed. Tissue samples are then collected, cut into small pieces (0.5–1.0 cm^2) and mounted on a glass slide with the stratum corneum facing the cover slide to be investigated optically. Confocal laser microscopy is particularly useful for the purpose. With rhodamine-labeled Transfersome vesicles, the stratum corneum penetration is detectable in vivo after 30–60 minutes and the label is recovered in greater quantity in epidermis or dermis 8–12 h later. Such experiments revealed the preferred path of vesicle penetration through the skin. This is always in the region of lowest skin penetration resistance and is located between corneocytes in the stratum corneum, most often at those sites where lipid multilayers are least tightly packed. Results obtained ex vivo with the same kind of skin differ in that label distribution is less uniform and the delivered material resides at the lower stratum corneum/viable epidermis boundary. This is another indication of the essential role played by the hydration gradient in the skin in the process of organ penetration by a Transfersome [20].

For transport rate measurements, fluid samples are collected and analyzed from the lower receiver compartment at different times. When analyzing the results of such experiments performed in vitro one must keep in mind that an excised skin sample simulates the real-life situation better than an artificial membrane with regard to the skin response to vesicle transport or driving force. A piece of skin tested in vitro does not fully reflect the physiological situation in vivo, however, owing to the lack of intercellular fluid motion in such tissue. In vivo experiments are therefore the only reliable method for studying Transfersome transport across the skin. Such experiments are also essential for pharmacokinetic investigations and even for skin penetration and body distribution studies [16]. In a representative example, Transfersome suspension labeled with ^{3}H-phosphatidylcholine were applied to intact murine skin or injected subcutane-

Copyright © 2003 Marcel Dekker, Inc.

ously. Radioactivity was measured as a function of time in the blood, dermis, three different muscles, kidney, liver, spleen, and several other organs. A rise in the muscle, kidney, and blood counts was accompanied by the decline of radioactivity in the skin. After 1 day, essentially the same radioactivity biodistribution was found for injected and epicutaneously applied Transfersomes. Transfersome-derived label appeared in the blood 4 h after test formulation application and increased in concentration over time reaching a plateau after 6–10 h. To study Transfersome-mediated drug delivery through the skin, in vivo experiments were carried out using ^{3}H- or ^{14}C-labeled drugs associated with the carriers. This showed that lipophilic low-molecular-weight drugs, such as testosterone (mol. wt. = 288) or triamcinolone acetonide (mol. wt. = 434.5) appeared in the blood at times comparable to those measured for the carriers. Similar results were found with the highly water-soluble calcitonin, heparin, or dextran, with respective molecular weights of 3432, 7500, or 70,000. These substances and serum albumin (mol. wt. = 64,000) were transported through the skin equally successfully indicating the lack of molecular size effect on Transfersome-mediated drug delivery through the skin (Fig. 5). Indeed, serum albumin was recovered in the blood with a distribution profile similar to that of testosterone, as judged on the basis of ^{125}I- or ^{3}H-radioactivity measurements.

Tests were also run with insulin in different Transfersome formulations in pigs and humans. Transfersome suspensions were prepared as described previously using regular, commercial recombinant human insulin (Actrapid, Novo-Nordis). The originally heterogeneous Transfersome preparation was homogenized to yield vesicles with radii of approximately 90–110 nm, which were filtered through a sterile 0.22-μm membrane filter. The final insulin concentration in the Transfersome preparation was 84 IU/mL or 40 IU/mL, respectively. Insulin associated with Transfersome carriers (Transfersulin®) (a trademark of IDEA AG) was applied epicutaneously in mice, pigs, and humans. The resulting blood glucose concentration changes were monitored as a function of time (Fig. 6). In addition, Transfersome carriers prepared with ^{125}I-labeled insulin were applied to the animals' skin to study tissue distribution of the insulin-derived radioactivity throughout the body with autoradiography [19]. Epicutaneous Transfersulin application lowered the blood glucose by 2–30%, starting at approximately 2 h after drug administration, whereas equally used preparations of insulin in mixed lipid micelles or liposome suspensions did not change the blood glucose level significantly. Similar data were measured in mice, pigs, and humans. The highest concentration of insulin-derived radioactivity was detected in urine, followed by the gastrointestinal tract, other soft tissues, and the blood. No significant differences between the results of epicutaneous and subcutaneous application were observed in biodistribution measurements, except for the lag time prolongation by 4–6 hours for the epicutaneous versus subcutaneous group.

The above-mentioned results show that insulin can be delivered successfully through the skin in Transfersome carriers, despite the high molecular weight

Copyright © 2003 Marcel Dekker, Inc.

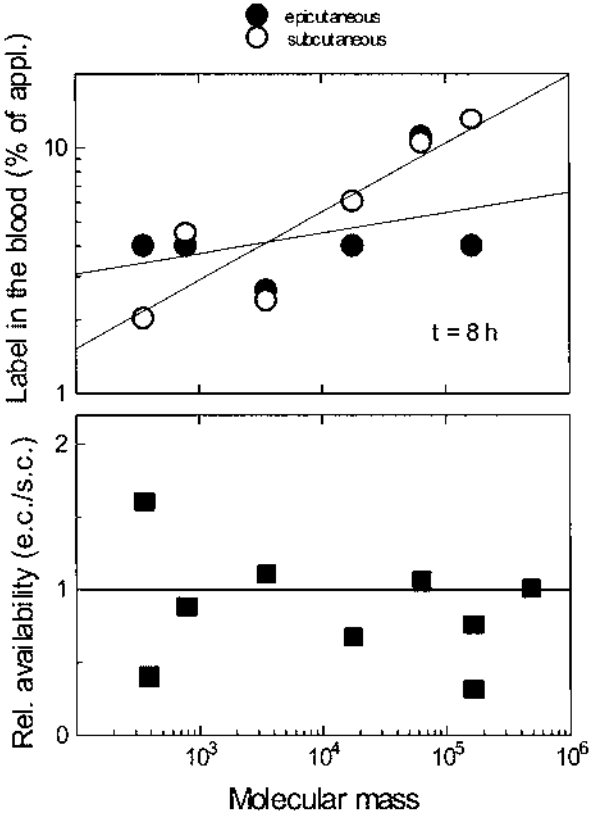


Figure 5 Relative efficiency of transcutaneous delivery with Transfersomes is little affected by the molecular mass of transported species, as demonstrated by directly comparing the results of epicutaneous (EC) and subcutaneous (SC) application of the test formulation.

of the drug (mol. wt. = 5808). This offers a promising noninvasive alternative to the long-acting depot injections of the drug. Transdermal insulin would also be useful in conjunction with the inhaled, rapidly acting insulin that is under development by several biotechnological companies (e.g., Inhale, Aradigm).

V. CURRENT AND FUTURE RESEARCH AND DEVELOPMENT

Almost 80 first-generation products based on classic transdermal drug delivery technologies are now on the market. Very few, however, have been added over

Copyright © 2003 Marcel Dekker, Inc.

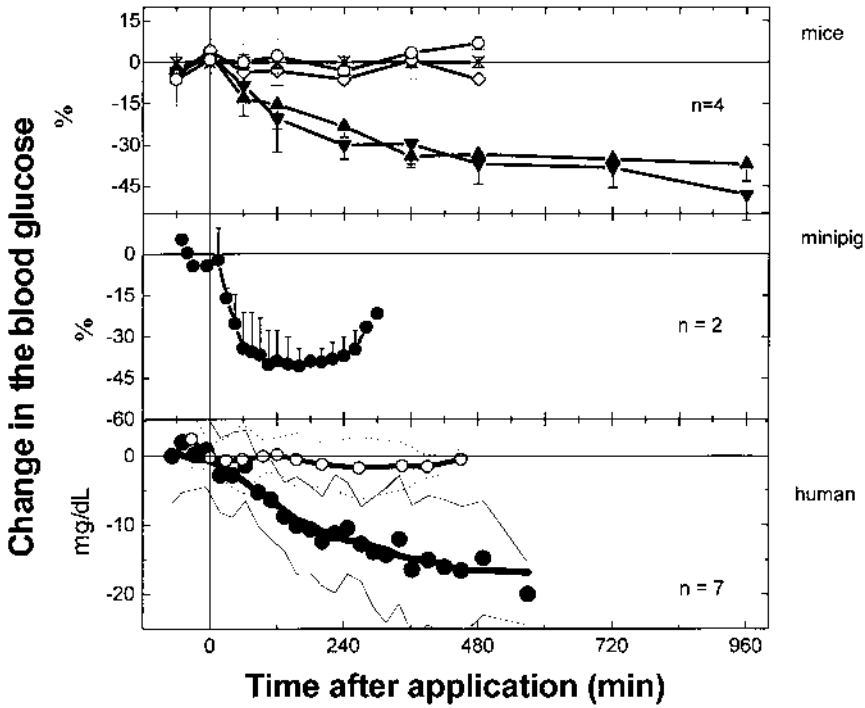


Figure 6 Glucodynamic effect of insulin delivered across the skin of mice, pigs, and humans by means of Transfersomes (closed symbols). Open symbols give the results of negative control experiments performed with mixed lipid micelles (open diamonds) or lipid vesicles (liposomes; open circles). (From Ref. [11].)

the last few years. Indeed, the last two decades have seen tremendous research efforts in the field of liposomes as transcutaneous drug carriers. Notwithstanding this fact, only two topical, lipid-containing products have reached the market—neither of which uses liposomes in the formulation. Transfersome carriers, the latest development in transcutaneous drug delivery, are not yet commercially available and need further development before reaching the market. It is expected that Transfersomes, like any other new drug formulation, will have to be tested extensively in vitro and in vivo before reaching the market.

IDEA AG, a company located in Munich, concentrates on innovative therapeutics based on Transfersome technology. At present, five projects in different developmental stages are under investigation. Interferon and tetanus vaccine are in the stage of preclinical development, but could soon enter the clinical phase. Triamcinolone acetonide (Fig. 7), a well-known glucocorticoid introduced on the

Copyright © 2003 Marcel Dekker, Inc.

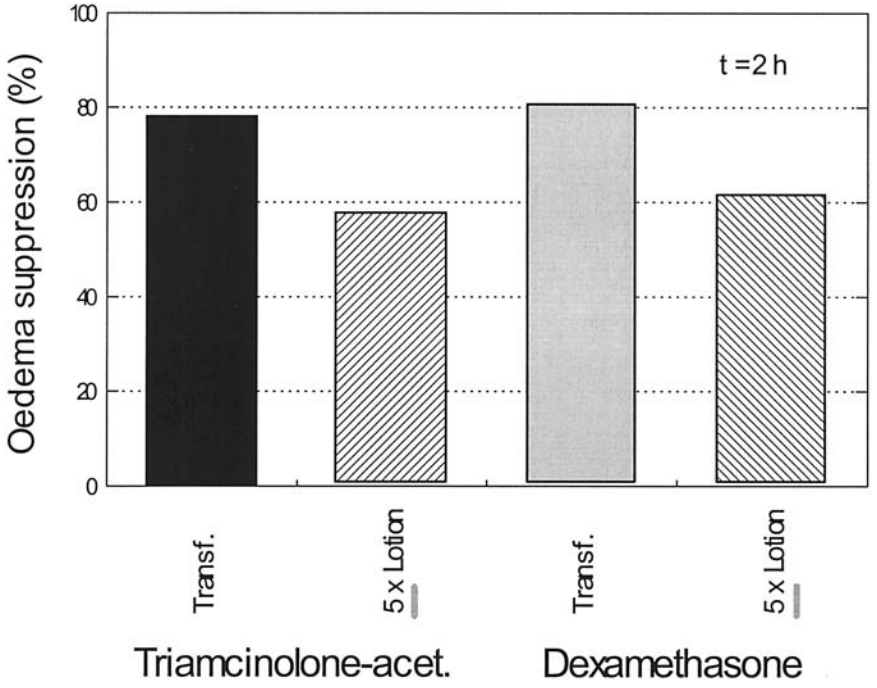


Figure 7 Triamcinolone acetonide and dexamethasone delivered with Transfersomes into the skin are biologically active, in a murine ear edema suppression test, at a much lower drug dose than when applied epicutaneously in a commercial lotion. (From Ref. [11].)

market more than 30 years ago, has successfully passed two clinical phase I studies in several Transfersome-based formulations, including one in which a generally recognized surrogate marker was measured. Further development will be influenced by the success or failure of the complementary inhaled insulin formulations. This extended Phase IIa studies with insulin in Transfersome carriers. Suspension was tested measuring the glucodynamic response to Transfersulin on the skin and to an injection of ultra-lente insulin Ultratard (Novo-Nordisk), used at a 4 times lower dose, revealed no significant difference between the two formulations. The tests done with an NSAID (non-steroidal anti-inflammatory drug), formulated with Transfersome carriers and used in several clinical Phase I and Phase IIa studies with more than 7000 people, confirmed the superior therapeutic potency of the drug in highly deformable carriers compared with two corresponding commercial products.

Copyright © 2003 Marcel Dekker, Inc.

VI. ADVANTAGES OF THE TECHNOLOGY

Intact skin has long been considered an interesting but very restrictive port of entry for bioactive materials into the body. This was seen as a natural consequence of biological optimization of this barrier. Transfersome carriers for the first time overcame this obstacle without unacceptably compromising the skin barrier. In contrast, standard pharmaceutical drug formulations, such as hydrogels, ointments, or creams, and also more modern formulations involving liposomes are of no practical use for the delivery of drugs across the skin into the systemic blood circulation. The addition of chemical skin permeation enhancers can improve the situation, but only for certain small drugs. Skin poration using electrical fields, ultrasound, thermal injury, or various ballistic methods (e.g., powder jection, high-velocity microdroplet impact) is less attractive owing to the long recovery period of the damaged skin and the danger of body infection through the lesion. The same is true for minipumps, which introduce small wounds in the skin through which the drug is continuously injected into the body.

Transfersome carriers therefore stand alone as very versatile and efficient, but also extremely gentle, drug carriers that can deliver a variety of agents, nearly independent of their size, structure, molecular weight, or polarity. They have the advantage of being made from pharmaceutically acceptable ingredients using standard methods, but need to be designed and optimized on a case-by-case basis. Use of Transfersome technology also requires unconventional thinking in the design of analytical methods. It can, but needs not, affect drug biodistribution, which can be used to advantage for tissue or region-specific targeting into the skin or subcutaneous and adjacent tissue targeting, respectively. Figure 8 provides an example for the latter.

Transfersome carriers applied on the skin are an obvious choice for achieving sustained drug release, the skin surface acting as a reservoir for the drug as well as the carriers. They should not be used for reaching high and rapid peak values, however, unless the skin at the application site is the administration target.

Transfersome vesicles applied on the skin in small quantity are "consumed" relatively rapidly and are deposited nearly exclusively in the skin proper. A 100–1000 times higher amount of epicutaneously administered carriers strongly favors systemic delivery. On the basis of relative drug distribution, intermediate doses have intermediate effects. No other system reported in the literature to date offers similar controllability.

VII. FUTURE DIRECTIONS

No drug delivery system has been perfected in a single step. Likewise, the Transfersome technology will evolve further. This relates not only to the use of self-

Copyright © 2003 Marcel Dekker, Inc.

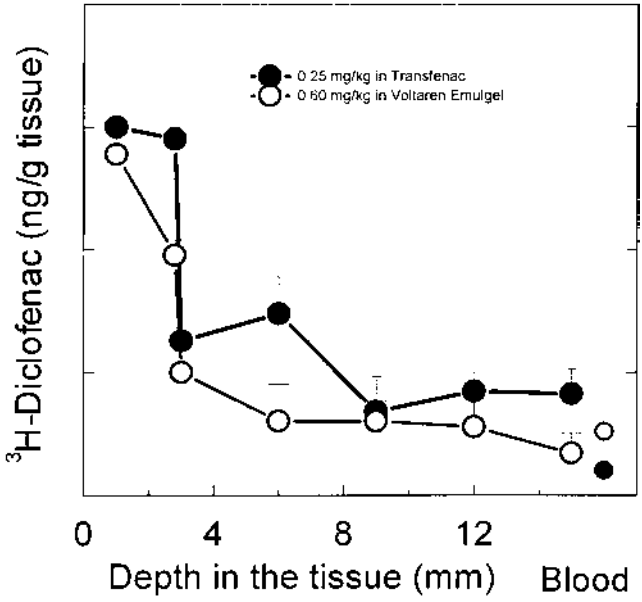


Figure 8

regulating carriers in different devices (patch, electrically controlled epicutaneous reservoir, etc.), but also to the design of carriers with additional special features that would, for example, allow targeting to cellular subsets or would be able to enter the brain.

REFERENCES

1. G Gregoriadis. Liposome Technology. 2nd ed. Boca Raton, FL: CRC Press, 1992.
2. DA Tomalia, AM Naylor, WA Goddard. Starburst dendrimers: molecular-level control of size, shape, surface chemistry, topology, and flexibility from atoms to macroscopic matter. Angw Chem Int Ed Eng 29:138–175, 1990.
3. G Cevc. Drug delivery across the skin. Exp Opin Invest Drugs 6:1887–1937, 1997.
4. G Cevc, G Blume. New, highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable drug carriers, Transfersomes. Biochim Biophys Acta 1514:191–205, 2001.
5. G Cevc, A Schätzlein, G Blume. Transdermal drug carriers: basic properties, optimization and transfer efficiency in the case of epicutaneously applied peptides. J Control Rel 36:3–16, 1995.

Copyright © 2003 Marcel Dekker, Inc.

6. G Cevc. Preparation for the application of agents in minidroplets. EU patent 0475160, 1996.
7. G Cevc. Electrically controlled transport of charged penetrants across barriers. PCT/EP 98/05539, 1998.
8. G Cevc. Method for developing, testing and using associates of macromolecules and complex aggregates for improved payload and controllable de/association rates. PCT/EP 98/06750, 1998.
9. G Cevc. Preparation for the transport of an active substance across barriers. PCT/EP 96/04526, 1996.
10. G Cevc. Preparation for drug application in minute droplet form. European patent EP 0475160, 1992.
11. M Mezei. Liposomes and the skin. In: G Gregoridadis, AT Florence, H Patel, eds. Liposomes in Drug Delivery. London: Harwood Academic Publishers, 1993, pp. 24–135.
12. ML Mezei. Liposomes as a skin drug delivery system. In: DD Breimer, P Speiser, eds. Topics in Pharmaceutical Sciences. Amsterdam: Elsevier, 1985, pp. 345–358.
13. R Schubert, M Joos, M Deicher, J Lasch. Mode of action of topically applied liposomes in dermatology and cosmetics. Proc MoBBEL 6:20–32, 1992.
14. D Raskovic, P Piazza. Liposomes: a promising future for dermato-cosmetology and clinical dermatology. J Liposome Res 3:737–751, 1993.
15. HEJ Hofland, R Vander Geest, JA Bouwstra, HE Bodde, HE Junginger. Estradiol permeation from non-ionic surfactant vesicles through human stratum corneum in vitro. Pharm Res 11:659–664, 1994.
16. G Cevc. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration and transdermal drug delivery. Crit Rev Ther Drug Carr Syst 13:257–388, 1996.
17. ME Planas, P Gonzales, L Rodriguez, S Sanchez, G Cevc. Noninvasive percutaneous induction of topical analgesia by a new type of drug carrier and prolongation of local pain insensitivity by anesthetic liposomes. Anesth Analg 75:615–621, 1992.
18. SI Simões. Libertação transdérmica de fármacos: vesículas lipídicas ultraflexíveis. PhD dissertation, IBQTY-INETI-Instituto Nacional de Engenharia e Technologia Industrial, Lisbon, Portugal, 2002.
19. G Cevc, D Gebauer, J Stieber, A Schätzlein, G Blume. Ultraflexible vesicles, Transfersomes, have an extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin. Biochim Biophys Acta 1368:201–215, 1998.
20. A Schätzlein, G Cevc. Non-uniform cellular packing of the stratum corneum and permeability barrier function on intact skin: a high-resolution confocal laser microscopy study using highly deformable vesicles (Transfersomes). Br J Dermatol 138: 583–592, 1998.

Copyright © 2003 Marcel Dekker, Inc.

45
Advances in Wound Healing

Michael Walker
ConvaTec Wound Care and Prevention Global Development Centre, Deeside, Flintshire, England

I. INTRODUCTION

The simple act of covering a wound, by whatever means, to effectively duplicate the function of the epidermis has been understood throughout history as a way of protecting that wound from the potentially harmful external environment. This chapter will focus on one aspect of wound healing, the recalcitrant nonhealing or "chronic" wound, i.e., leg ulceration, as the subject matter of wound healing per se is beyond the scope of this chapter. Throughout this chapter the words "chronic wound" and "leg ulcer(ation)" will be used interchangeably. Chronic wounds are generally considered to have resulted from endogenous circumstances, although it is well recognized that exogenous conditions such as bacterial infection or radiation can induce skin lesions.

Historical evidence will be presented to highlight that the most significant advances in the understanding of the pathophysiology of chronic wounds have been made over the last 50 years. The problem now is that the clinician, nurse, and patient are overwhelmed with a plethora of new products all claiming wound-healing benefits.

In particular this chapter will outline some of the opportunities and pitfalls associated with developing a topical application for chronic wounds, including the use of pharmacological agents, and how not only is choice of delivery vehicle important, but interactions of secondary dressings may also play a role.

Finally, a brief overview of future opportunities will be proposed emphasizing there can be no "silver bullet" approach and any new advances must consider the financial constraints on national health care systems. Thus there is a need to obtain a balance between best possible clinical care/practice and affordable qual-

Copyright © 2003 Marcel Dekker, Inc.

ity products that may lead to a healed wound or an improved quality of life for individual patients.

II. HISTORICAL DEVELOPMENT

Various medicaments have been recorded since early Egyptian times, yet it is Hippocrates who has been credited with one of the earliest mentions of chronic wounds as he apparently recognized some relationship between leg ulceration and venous disorders [1]. As early as the tenth century there was widespread belief that to cure an ulcer prevented the efflux of dangerous humours [2], which was widely upheld until the eighteenth century. In a recently discovered early-fifteenth-century manuscript, chronic wounds, regardless of cause, were divided into seven classes of ulceration based on a Latin nomenclature [3]. The classes ranged from *corrosium*, a wound that slowly progresses to form a shallow cavity prior to healing, through *virulentum*, an old wound in which exudate is liquid and plentiful, to *difficillis consolidationis*, an old wound that is difficult to heal, but not a cancer or an inflamed sore [3].

In 1775 the physician John Hunter wrote that "the sores of poor people are often in a bad condition from bad living and are often healed by rest in a horizontal position, fresh provisions and warmth in hospitals, and the change is generally very speedy" [4]. Another significant contribution to present knowledge was made by John Gay in 1867 when he described not only clot formation and post-thrombotic recanalization, but also recorded that ulceration could occur in the absence of varicose veins and introduced the term "venous ulcer" [5].

Perhaps the most significant advances in both the understanding of chronic wound pathophysiology and the introduction of modern wound dressings have taken place within the last 40–50 years. Table 1 highlights the historical development of wound treatments and illustrates how these regimens have improved with our greater understanding of chronic wound biology.

III. A TOPICAL PRODUCT FOR WOUNDS: IMPORTANT CONSIDERATIONS

In acute wounds healing takes place via a well-defined series of steps, with each phase dependent upon the normal progression of the previous phases. If an abnormality in any one phase occurs, it may result in abnormal or impaired healing, fibrosis, or ulceration. Until fairly recently the accepted clinical dogma had been that chronic wounds were static and required stimulation, hence the major research undertaken to develop topical growth factors. Thus very few pharmacotherapeutic products are now available that are used specifically to treat chronic

Copyright © 2003 Marcel Dekker, Inc.

Table 1 The Historical Development of Wound Treatments

Year	Treatment	Reference
1600 B.C.	Grease, honey, lint, castor oil—Egyptians—Smith papyrus	[6]
~ A.D. 1–200	Plaster, linen bandages—Celus/Galen–initial concept of "laudable pus"	[7,8]
1000–1700	General belief maintained throughout this period: "to cure an ulcer was to prevent the efflux of dangerous humours"	[2]
1000–1100	Promotion of per secundum intentionem by promoting the production of pus	[9]
1200–1300	Bandages soaked in wine—per priman intentionem, without infection	[9]
1400–1500	Practice of wound cautery, i.e., burning oil/hot irons—Paracelcus	[5]
~1500	Ligation introduced by Parc; general use of ointments, bandages, and cotton lints	[9]
~1600	Blood cupping = release of blood through the skin—Schropfkopf + cutting glass	[9]
1676	First description of a laced stocking	[10]
~1700	Introduction of compression bandages for old sores and edema; bandages were usually made out of linen, wool, silk, or parchment	[11]
1870s	Development of rubber bandages—Martin	[9]
1920s	Elastoplast released onto the market	
1960s	Concept of moist wound healing developed—Winter studies → UK registration of Opsite™ first occulsive dressing	[12] [13]
1980s	Development of Hydrocolloids (e.g., Granuflex™), Foams (e.g., Alleyn™), and Hydrogels (e.g., Intrasite™)	
1990s	Development of Alginates (e.g., Sorbsan™, Hydropolymers (e.g., Tielle™), and Hydrofibres (e.g., Aquacel™)	
2000+	Development of biopolymer materials, e.g., Hyalofil™, an esterified hyaluronic, acid biopolymer, and therapeutic agents, e.g., drugs—Regranex™	
	Possible development of biomaterials and use of tissue engineering?	

wounds. However, two major areas of development are the emerging importance of drug delivery systems in tissue engineering and the use of bioactive materials, which have been recently reviewed by Tabata [14] and Hubbell [15], respectively.

The concept of wound pharmacology has been around for many centuries and was recently given a new definition: "the study of agents and their actions in

Copyright © 2003 Marcel Dekker, Inc.

the wound environment" [16]. There are many advantages in considering topical therapy over oral delivery as it is possible that an oral drug may not be delivered to the site of action in sufficient quantities to bring about a therapeutic response. Care must also be taken in defining the target site, as to whether the drug needs to reach the wound/local tissue or the localized capillary circulation. It has been suggested that "it is logical to treat a local pathological lesion with a local therapy, provided that the agent is delivered effectively and safely to the target organ or tissue" [17]. Localized delivery has many advantages and has been defined as the local accumulation in a target tissue of a pharmacological agent in greater concentrations than that expected to have resulted from systemic redistribution through the local vasculature [18].

Despite these obvious advantages, the biology of the wound also has a major role to play. By definition a chronic wound does not have an epithelium present, although as wound healing begins the presence of a newly formed or partly formed epithelium may affect drug delivery [18]. Other factors include the active discharge of wound fluid and how this may influence the passive movement of a therapeutic agent as it is released from its vehicle. Molecular weight of an active therapeutic agent and wound depth have recently been shown to be significant determinants in the partitioning and tissue distribution of the drug [19]. The vehicle itself must be carefully formulated to reduce the problems associated with contact sensitivity and skin irritation [20]. Therefore, when considering a topical product for a wound, there needs to be a much greater awareness of known excipients that are commonly used in topical products for normal skin, but that are considered allergens to leg ulcer patients, e.g., wool alcohols and certain preservatives [21].

In conventional wound therapy, a modern wound dressing is applied directly to the wound site to absorb wound exudates, such that if a topical treatment is to be considered, a secondary dressing will always be present. The physical/chemical composition of this dressing may influence the rate of drug delivery to the desired site as the drug may be carried away from the wound site and into the dressing, via the exudates, thus reducing its availability for release.

The use of topical agents, i.e., drugs, may inhibit as well as assist in the wound-healing process. Any therapeutic effect may be affected by dosage, route of administration, and, perhaps most important, mechanism of action. Table 2 highlights some of the drugs that have been used in wound healing, and Karukonda and co-workers have recently published two articles reviewing the effect of drugs on wound healing [22,23].

It is beyond the scope of this chapter to discuss the many drugs that may prove advantageous to wound healing but two important aspects have been selected for more detailed discussion: the role of the vehicle and how dressing materials may influence drug delivery. A novel thromboxane receptor antagonist (Ifetroban), has been utilized as an example of a hydrophilic drug molecule to

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Drugs and Their Effects on Wound Healing

Pharmacotherapeutic agent	Effect on wound healing
Anti-inflammatories	Reduce inflammation, tissue remodeling
Corticosteroids	Inhibit gene expression of various cells Reduce cytokine expression and presence of macrophages and platelets Affect collagen remodeling
Colchicine	Effect neutrophil expression of cell adhesion receptors
Dapsone Antimalarials	Reduce inflammation without significant immunosuppression.
Immunosuppressants Azathioprine Methotrexate Cyclosporin	In general, no significant inhibition of wound healing
Retinoids Tretinoin Isotretinoin Vitamin A	Effect both epithelialization and angiogenesis
Antimicrobials	
(a) Antiseptics	Can induce tissue necrosis and increased inflammation
Povidine iodine Hexachlorophene Chlorhexidene	In general, they all retard epithelialization and sometimes wound contraction Should only be used on infected wounds
(b) Antibiotics	
Neomycin	May get allergen contact dermatitis with topical antibiotics
Gentamicin Mupirocin Silver sulfadiazine	Prolonged use may result in resistance
Vascular drugs	
(a) Anticoagulants Coumarin Heparin Warfarin	Prevent fibrin deposition and in general reduce the risk of venous thrombosis
(b) Antiplatelets	
Aspirin	Prevent platelet activation and aggregation, reducing thrombus risk
Nonsteroidals, e.g., Paroxican, indomethacin	General anti-inflammatory effects by mediating archadonic acid metabolites Improve blood circulation by reducing blood viscosity
(c) Hemorrheologics Pentoxifylline (Trental)	May be helpful in some connective tissue diseases, i.e., restoring blood flow, as in Raynaud's disease
(d) Vasodilators Nifedipine Ketanserin	Can cause tissue hypoxia; smoking should be avoided to reduce risk of poor healing
(e) Vasoconstrictors Epinephrine Nicotine	

Source: Adapted from Ref. [23].

Copyright © 2003 Marcel Dekker, Inc.

illustrate how vehicle and dressings may influence its delivery. This drug was originally considered for topical application as thromboxane A_2 and its endoperoxide precursors are potent vasoconstrictors and platelet activators and were thought to play an important role in vasculoinflammatory activation, which is a characteristic pathology of chronic wounds [18].

IV. THE ROLE OF THE VEHICLE

Choosing the correct vehicle is very important, not only as a sensitization/irritation issue, as previously discussed, but the thickness of the applied vehicle [24] and its composition [25] can influence the delivery of a desired therapeutic agent. Figure 1 demonstrates how vehicle composition can affect drug release.

Using a modified Franz diffusion cell system with a dialyzing membrane (mol. wt. cutoff 12 Kda), it was shown that when the drug was placed in an ointment formulation, the release profile was very poor (<5% over a 50-h period). The use of an aqueous hydrocolloid gel improved the release, but it was evident that vehicle application thickness could also influence the release of the active ingredient from the gel. In the original studies, approximately 300 mg was applied to the dialysis membrane surface, whereas if only approximately 50 mg was ap-

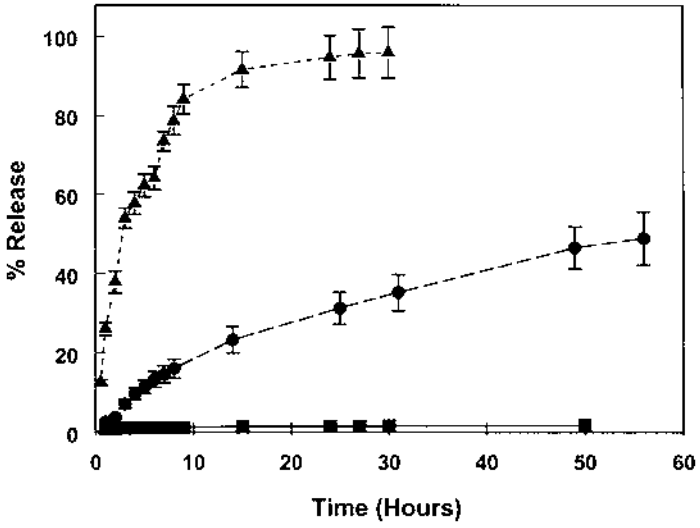


Figure 1 Drug release profiles from various formulations: ointments (■); thick gel application (●); thin gel application (▲).

Copyright © 2003 Marcel Dekker, Inc.

plied, which is more applicable to the clinical situation, over 75% was observed to be released within the first 8 h, culminating in almost 100% release within 30 h. One explanation for this may be that water is absorbed into the thinner formulation faster allowing more rapid release of the drug due to alterations of the solvent-polymer cross-linking ratio.

V. THE ROLE OF A SECONDARY DRESSING MATERIAL IN DRUG DELIVERY

If a topical product is to be applied to a wound, it would be covered with a secondary dressing, and its composition may directly influence the release and/or delivery of the drug to its target site. Most wounds discharge wound exudates and this represents an active gradient against the passive movement of the drug from the vehicle to the target site. If the dressing has good exudate-handling properties, it is possible that some of the drug may be carried with the exudates away from the wound site and back into the dressing.

To illustrate this point, Figure 2 shows how the application of different secondary dressings applied on top of an aqueous hydrocolloid gel preparation can affect drug release. Gauze is the traditional dressing that is applied to a

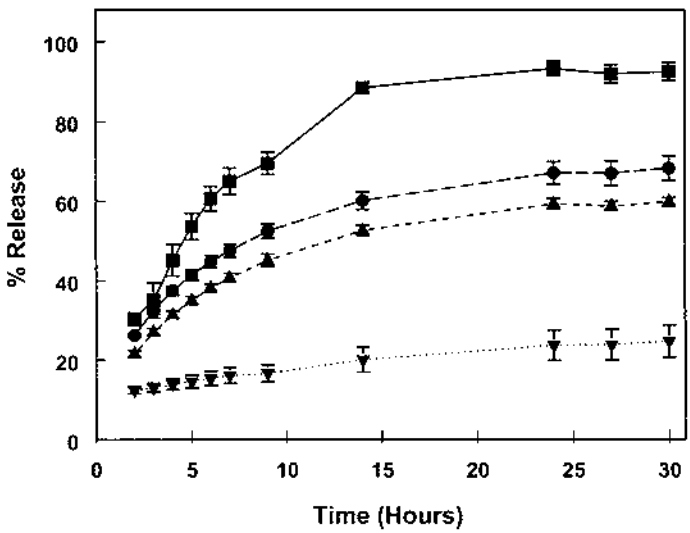


Figure 2 Influence of secondary dressing on drug release profile: no dressing (■); Kaltostat (●); Sorbsan (▲); gauze (▼).

Copyright © 2003 Marcel Dekker, Inc.

wound, yet in these studies the drug release profile was poor. The gel was observed to be very quickly absorbed onto the gauze dressing forming a thin film. It was assumed that water evaporating from the gel caused a reduction in volume and contact may have been lost from the membrane surface, hence the poor release profile. In comparison, two alginates, Sorbsan™ and Kaltostat™, were tested as these have different compositions and consequently different fluid-handling characteristics. Sorbsan has a high mannuronic content and is considered a calcium alginate with good initial absorbency, but poor cohesion when fully saturated, whereas Kaltostat has a high glucuronic content and has sodium replacing some of the calcium, which gives it greater absorbency with time and increased tensile strength. These differences in chemical structure perhaps help explain the differences in release profiles seen in Figure 2. Sorbsan has the ability to absorb water rapidly and may extract water from the gel, slowing down release of the drug from the gel, whereas Kaltostat, having a slower rate of water uptake, ensures that more drug can be released with time.

It is important to understand that the choice of secondary dressing may influence drug delivery and, through the use of occlusion, actually improve drug delivery [26].

VI. REGULATORY ISSUES

Regulatory authorities are now reviewing the application of a topical agent to a wound site on a case-by-case basis [27,28]. Therefore, it is important that pharmacokinetic/pharmacodynamic and toxicological studies are undertaken. In particular, both systemic and local toxicity issues need to be considered for any wound treatment regimen. It is important to recognize that tests on normal volunteers for issues such as contact sensitivity will probably be a severe underestimation [20] as many elderly patients appear to have single or multiple sensitivities to many topical agents [21].

It has been suggested that therapeutic drug monitoring should be performed whereby a potential therapeutic agent's activity could be optimized by adjusting dosage regimens to coincide with the stages of wound healing [16]. This may require the use of an appropriate model in the early stages of development. This is a very important consideration in that the model truly reflects the clinical situation. Ideally the true model is a human wound, but performing clinical trails is often prohibitively expensive. It has been suggested that tissue penetration assays should be performed as part of the preliminary screening process, and dermal membranes have recently been suggested as a suitable in vitro model [18]; Cross and Roberts have used an in vivo rat model to investigate drug distribution in localized areas following topical application [19]. Gottrop et al. have recently published a comprehensive review on the use of models in wound healing [29].

Copyright © 2003 Marcel Dekker, Inc.

Table 3 Topical Drug Applications that Have Been Used in Clinical Trials

Therapeutic agent	Treatment	Ref.
Bercaplermin (Regranex™)	Pressure sores	[31]
	Mixed arteriovenous-diabetic ulcers	[32]
Autologous platelet-derived growth factor	Venous leg ulcers	[33]
Recombinant basic fibroblast growth factor	Diabetic/neuropathic ulcers	[34]
Recombinant human granulocyte, macrophage-colony-stimulating growth factor	Venous ulcers	[35]
Recombinant tissue plasminogen activator in hyaluronic acid gel	Venous leg ulcers	[36]
Hyaluronic acid	Venous leg ulcers	[37]
Ticlopidine	Ischemic ulcers	[38]
Low-molecular-weight heparin	Ischemic arterial ulcers	[39]
Pentoxyfilline	Venous leg ulcers	[40]
Prostacyclin	Leg ischemia	[41]
Essential fatty acids	Pressure sores	[42]
Hyperbaric oxygen	Necrotic/gangrenous ulcers	[43]

Many new products under consideration are from naturally occurring substances such as carbohydrates (hyaluronic acid) and proteins (growth factors) whereby these products have been suitably modified, e.g., esterification of Hyaluronan [30], or synthetically produced, e.g., recombinant platelet growth factor, Regranex™ [31,32]. Many similar products have reached clinical trials (Table 3), yet very few have actually proved successful in the marketplace.

Another important issue is how different regulatory authorities view certain wound-healing products. For example, a composite dressing that contains human cells is defined as a device in the United States, a biological in England, and may not even be allowed to be sold in certain parts of Europe, e.g., France. Clinical trial end-points are another example of how Europe and the United States have opposing views. In Europe there is a tendency to allow a range of outcomes other than complete healings, whereas the Food and Drug Administration (FDA) suggests an ideal end-point is the number of wounds healed related to time. Products in Europe have to be terminally sterilized and are single dose/single patient usage. In the United States most products do not need to be terminally sterilized and many are sold in multidose or multipatient containers. All these issues are important factors that need to be considered before a successful product can be made available to the clinician or caregiver.

Copyright © 2003 Marcel Dekker, Inc.

VII. FUTURE OPPORTUNITIES FOR ADVANCES IN WOUND HEALING

Within the last 10 years an unprecedented proliferation has occurred in the number of wound care products that are available, and with the advances now being made in genetic engineering, it may be possible to target biological mechanisms with a specific pharmacological intervention. In the field of biomaterials, important advances have been made with a move away from simple chemical degradation, e.g., ester hydrolysis, to a more sophisticated approach whereby it may be possible to allow a more bioactive degradation based on cellular feedback [15]. This is essentially what happens in nature as new tissue is generated or remodeled by enzymatic degradation of the surrounding extracellular matrix.

At present no unified biological mechanism is available to fully explain chronic wound pathophysiology, yet there is a much greater understanding than there was several years ago, although it has been suggested that there is still a gap between good laboratory research and clinical practice [44]. There is increasing interest in the area of tissue engineering in that natural tissues may be regenerated or biological substitutes produced through the use of cells [14]. Tissue regeneration has now been elucidated at both the genetic and cellular levels and stem cells have been shown to play a key role [45].

Both of these methods are still very much in their respective infancy in terms of providing a clinical impact and the expenses associated with them may yet prove inhibitory. There will also be more stringent regulatory control over such products and great advantages in safety and efficacy must be seen to compensate for the high cost of development and subsequent use of such products.

Another important issue is the decisions made by health professionals with respect to patient management and their quality-of-life issues, especially with the increasing longevity of human life and the fact that the majority of chronic wounds are rarely life threatening. As outlined at the beginning of this chapter, there will be "no silver bullet" answer to the healing of a chronic wound, and no doubt, for the foreseeable future the emphasis will resolve around antiprotease and growth factor therapies.

Perhaps one of the most important problems is educating the appropriate people to stop using ineffective or possibly harmful products. These include toxic wound-cleaning agents, random use of antibiotics, and the use of wet-to-dry dressings. Often a caregiver or clinician is presented with an overwhelming choice of wound care products, few of which have been proven to be better than much simpler and more cost-effective treatments. Equally there is a growing need to address the cost of expensive drugs against health care budgets. They have to be clinically proven to be cost-effective before many health care authorities would consider such an option. Finally, there can be few medical conditions that

Copyright © 2003 Marcel Dekker, Inc.

have produced so many diverse treatments, prompting the comment "It is to be hoped that one day someone will discover something that works!"

REFERENCES

1. Hippocrates. De ulcerbis, De carnabus. In: F Adams, ed. The Genuine Works of Hippocrates. London: Sydenham Society, 1849.
2. Avicenna. De ulceribus, Liber IV. Quoted by M Underwood. In: A Treatise on Ulcers of the Legs. London: Matthews, 1783.
3. Manuscript number 564, Western Manuscripts Collection on Medicine and Science, Wellcome Institute Library, London.
4. J Hunter. Observations on the inflammation of the internal coats of veins (1775). In: JI Palmer, ed. The Works of John Hunter. London: Longman, Rees, Orme & Longman, 1837, pp. 581–586.
5. J Gay. On varicose disease of the lower extremities and its allied disorders. Lettsomian Lectures of 1867. London: Churchill, 1868.
6. BR Reed, RAF Clark. Cutaneous tissue repair: practical implications of current knowledge. II. J Am Acad Dermatol 13:919–941, 1985.
7. AAC Celsus. Of Medicine, in Eight Books (translated by James Grieve; revised by George Futuoge). London: Renshaw, 1838.
8. C Galen. Ad scripti libri. Venice: Vincentium Valgressium, 1562, pp. 34. Quoted by ST Anning. In: H Dodd, F Cockett, eds. The Pathology and Surgery of the Veins of the Lower Limb. London: Churchill Livingstone, 1976, pp. 4.
9. A Scholz. Historical aspects. In: W Westerhof, ed. Leg Ulcer: Diagnosis and Treatment. Amsterdam: Elsevier, 1993, pp. 5–15.
10. R Wiseman. Several Chirurgical Treatises. London: Wilthoe & Knapton, 1676.
11. JCA Theden. Neue Bermerkungen und Erfahrungen zue Beriecherung der Wundarzenykunst und Arzenygelahrteit, Vol. 2. Berlin: Nicolai, 1782.
12. GD Winter. Formation of the scab and re-epithelialisation of superficial wounds in the skin of the young domestic pig. Nature 193:293–294, 1962.
13. DE Seymour, N Da Costa, M Hodgson, J Dow. Adhesive materials patent specification. UK patent #12800631, 1972.
14. II Tabata. The importance of drug delivery systems in tissue engineering. Pharm Sci Technol Today 3:80–89, 2000.
15. JA Hubbell. Bioactive biomaterials. Curr Opin Biotechnol 10:123–129, 1999.
16. F Arnold, G Cherry, D Cox, JJ Hutchinson, W Weston-Davies. Wound pharmacology: a report from the wound pharmacology forum. Wound Rep Reg 4:121–126, 1996.
17. R Grahame. Transdermal non-steroidal anti-inflammatory agents. Br J Clin Pract 49:33–35, 1995.
18. M Walker, TA Hulme, MG Rippon. In vitro model(s) for the percutaneous delivery of active tissue repair agents. J Pharm Sci 86:1379–1384, 1997.
19. SE Cross, MS Roberts. Defining a model to predict the distribution of topically

Copyright © 2003 Marcel Dekker, Inc.

applied growth factors and other solutes in excisional full-thickness wound. J Invest Dermatol 112:36–41, 1999.
20. CL Wilson, J Cameron, SM Powell. High incidence of contact dermatitis in leg ulcer patients—implications for management. Clin Exp Dermatol 16:250–253, 1991.
21. J Cameron. The importance of contact dermatitis in the management of leg ulcers. J Tissue Viab 5:52–55, 1995.
22. SRK Karukonda, TC Flynn, EE Boh. The effects of drugs on wound healing. Part I. Int J Dermatol 39:250–257, 2000.
23. SRK Karukonda, TC Flynn, EE Boh. The effects of drugs on wound healing. Part II. Specific classes of drugs and their effects on healing wounds. Int J Dermatol 39: 321–333, 2000.
24. PA Puolakkainen, DR Twardzik, JE Ranchalis. The enhancement in wound healing by transforming growth factor-β_1 (TGF-β_1) depends on the topical delivery system. J Surg Res 58:321–329, 1995.
25. M Walker, LA Chambers, DA Hollingsbee, J Hadgraft. In vitro delivery of halcinonide: significance of applied vehicle quantity to skin penetration. In: RC Scott, RH Guy, J Hadgraft, HE Boddé, eds. Predictions of Percutaneous Penetration: Methods, Measurements, Modelling. Vol. 2. Oxford, UK: IBC Technical Services, 1991, pp. 527–532.
26. DA Hollingsbee, RJ White, PAD Edwardson. Use of occluding hydrocolloid patches, in percutaneous penetration enhancers. In: EW Smith, HI Maibach, eds. Percutaneous Penetration Enhancers. Boca Raton, FL: CRC Press, 1995, pp. 35–43.
27. K Weiss, JP Segel, TL Gerrard. Regulatory issues in clinical applications of cytokines and growth factors. Prog Growth Factors Res 5:213–222, 1994.
28. K Stromberh, MS Chapekar, BA Goldman. Regulatory concerns in the development of topical recombinant ophthalmic and cutaneous wound healing biologics. Wound Rep Reg 2:155–164, 1994.
29. F Gottrop, MS Agren, T Karlsmark. Models for use in wound healing research: a survey focusing on in vitro and in vivo adult soft tissue. Wound Rep Reg 8:83–96, 2000.
30. L Ruiz-Cardona, YD Sanzgiri, LM Benedetti. Application of benzyl hyaluronate membranes as potential wound dressings: evaluation of water vapour and gas permeabilities. Biomaterials 17:1639–1643, 1996.
31. RS Rees, MC Robson, JM Smiell. Becaplermin gel in the treatment of pressure sores: a phase II randomised, double-blind, placebo controlled study. Wound Rep Reg 7:141–147, 1999.
32. MS Miller. Use of topical recombinant human platelet-derived growth factor-BB (becaplermin) in healing of chronic mixed arteriovenous lower extremity diabetic ulcers. J Foot Ankle Surg 38:227–231, 1999.
33. H Reutter, S Bort, MF Jung. Questionable effectiveness of autologous platelet growth factors (PDWHF) in treatment of venous ulcers of the leg. Hautarzi 50:859–865, 1999.
34. JL Richard, C Parer-Richard, JP Daures. Effect of topical basic fibroblast growth

Copyright © 2003 Marcel Dekker, Inc.

factor on the healing of chronic diabetic neuropathic ulcer of the foot. A pilot, randomized, double-blind, placebo-controlled trial. Diabetes Care 18:64–69, 1995.
35. E Jaschke, A Zabernigg, C Gattringer. Recombinant human granulocyte-macrophage colony-stimulating factor applied locally in low doses enhances healing and prevents recurrence of chronic venous ulcers. Int J Dermatol 38:380–386, 1999.
36. V Falanga, P Carson, A Greenberg. Topically applied recombinant tissue plasminogen activator for the treatment of venous ulcers: preliminary report. Dermatol Surg 22:643–644, 1996.
37. JP Ortonne. A controlled study of the activity of hyaluronic acid in the treatment of venous leg ulcers. J Dermatol Treat 7:75–81, 1996.
38. T Katsumura. Therapeutic effect of Ticlopidine for ischaemic leg ulcers: agents and actions. Suppl, Ticlopidine: Quo Vadis 15:167–172, 1984.
39. O Gauthier. Efficacy and safety of CY 216 in the treatment of specific leg ulcers. In: K Breddin, J Freed, M Samama, eds. Fraxiparine: Analytical and Structural Data, Pharmacology; Clinical Trials. Stuttgart: Schattaver, 1987, pp. 21.
40. MP Colgan, JA Dormandy, PW Jones. Oxypentifylline treatment of venous ulcers of the leg. Br Med J 300:972–975, 1990.
41. JN Fiessinger, M Schäfer. Trial of Iloprost versus aspirin treatment for critical limb ischaemia of thromoangiitis obliterans. Lancet 335:555–557, 1990.
42. V Declair. The usefulness of topical application of essential fatty acids (EFA) to prevent pressure sores. Ostomy Wound Manage 43:48–52, 54, 1997.
43. MC Heng, J Harker, VB Bardakjian. Enhanced healing and cost effectiveness of low pressure oxygen therapy in healing necrotic wound: a feasibility study of technology transfer. Ostomy Wound Manage 46:52–60, 62, 2000.
44. P Ferretti, J Géraudie. Cellular and Molecular Basis of Regeneration: From Invertebrates to Humans. Chichester, UK: John Wiley & Sons, 1997.
45. JJ Tomasek, G Gabbiani, B Hinz. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol 349–363, 2002.

Copyright © 2003 Marcel Dekker, Inc.

46

Ultrasound-Mediated Transdermal Drug Delivery

Samir Mitragotri
University of California, Santa Barbara, California, U.S.A.

Joseph Kost
Sontra Medical Inc., Cambridge, Massachusetts, U.S.A.

I. INTRODUCTION

Transdermal drug delivery offers several advantages over traditional drug delivery systems such as oral delivery and injection, especially in regard to protein delivery [1]. Transdermal drug delivery, however, suffers from the severe limitation that the permeability of the skin is very low. Therefore, it is difficult to deliver drugs across the skin at a therapeutically relevant rate. A possible solution to this problem is to increase the permeability of the skin using physicochemical driving forces, referred to as penetration enhancers, for example, chemical enhancers and electric fields [2]. In this chapter, we describe the use of low-frequency ultrasound (20 kHz $< f <$ 100 kHz) for delivering drugs across the skin.

II. HISTORICAL DEVELOPMENT

Ultrasound under a variety of conditions has been used for enhancing transdermal drug transport [3–25]. This phenomenon is referred to as sonophoresis. Some of the earliest studies of sonophoresis were performed using hydrocortisone. In 1954 Fellinger and Schmidt [26] reported successful treatment of polyarthritis of the hand's digital joints using hydrocortisone ointment with sonophoresis. Since that

* *Current affiliation*: Ben Gurion University, Beer-Sheeva, Israel.

Copyright © 2003 Marcel Dekker, Inc.

time, several sonophoresis studies have been reported using more than 10 drugs. Among the various frequencies that have been used for sonophoresis, therapeutic frequencies (1–3 MHz) correspond to the most commonly used conditions employed in over 90% of previous studies [27]. Typical enhancements induced by therapeutic ultrasound are less than 10-fold and are observed mostly for low-molecular-weight drugs. We have shown that ultrasound at a frequency of 20 kHz enhances transdermal transport of drugs more effectively than therapeutic ultrasound, a phenomenon referred to as low-frequency sonophoresis [16,28]. Low-frequency ultrasound has a clear advantage over therapeutic sonophoresis in that cavitational effects, which are responsible for low-frequency sonophoresis, are inversely proportional to ultrasound frequency [29]. In view of this, we focus on sonophoresis in the low-frequency region (20 kHz $< f <$ 100 kHz).

III. DESCRIPTION OF THE TECHNOLOGY

Low-frequency sonophoresis corresponds to the use of ultrasound at a frequency lower than 100 kHz for sonophoresis. Low-frequency sonophoresis can be divided into two types: (a) continuous application of ultrasound during drug delivery and (b) pretreatment of skin using ultrasound prior to drug delivery. Below, we discuss each of them.

A. Continuous Sonophoresis

This approach corresponds to simultaneous application of drug and ultrasound to the skin. This method enhances transdermal transport in two ways: (a) enhanced diffusion through structural alterations of the skin and (b) convection induced by ultrasound. Indeed, application of low-frequency ultrasound at 20 kHz enhances transdermal transport of various low-molecular-weight drugs as well as of high-molecular-weight proteins such as insulin across human skin. Skin permeability during low-frequency sonophoresis measured in vitro using human cadaver skin is up to 1000-fold higher than that in the absence of ultrasound [28]. Transdermal transport enhancement decreases after ultrasound is turned off. Thus, this method of enhancement may be used to achieve a temporal control over transdermal transport. Ultrasound conditions used for this type of sonophoresis correspond to low intensity (about 1 W/cm^2) and low duty cycle (for example, 10%). This method has been tested in vitro using human cadaver skin and in vivo with rat and pig skin using a variety of low-, as well as high-, molecular-weight solutes [16,28]. In particular, this method has been tested in vivo for transdermal insulin delivery and in vitro for delivery of erythropoietin and γ-interferon. Although this method may be used to achieve a temporal control over skin permeability, it requires that the patients use a wearable ultrasound device for drug delivery.

Copyright © 2003 Marcel Dekker, Inc.

B. Pretreatment

In this method, a short application of ultrasound is used to permeabilize skin prior to drug delivery. The skin remains in a state of high permeability for several hours. Drugs can be delivered through permeabilized skin during this period. Ultrasound conditions used for this type of sonophoresis correspond to relatively high intensities and low application times. Specifically, it has been shown that ultrasound (20 kHz, ~7 W/cm^2) increases skin permeability by up to 100-fold for a period exceeding 10 h [21,30]. This method has been tested for delivery of several low-, as well as high-, molecular-weight solutes. Specifically, it has been shown that macromolecules including insulin and low-molecular-weight heparin can be delivered across rat skin in vivo [30,31]. In this approach, the patient does not need to wear the ultrasound device. Instead, the device can be placed on the skin for a short time followed by the placement of a patch.

IV. RESEARCH AND DEVELOPMENT

In this chapter, we primarily discuss the pretreatment type of low-frequency sonophoresis. In this method, a short application of ultrasound is used to permeabilize skin. Skin remains permeable for extended times (~24 h). Enhanced skin permeability is monitored using skin conductivity. Skin conductivity is an excellent indicator of its permeability [21]. This occurs since the lipid bilayers of the stratum corneum (SC), which offer electrical resistance to the skin, also retard transdermal transport of molecules. The relationship between skin permeability and skin conductivity can be mathematically explained based on the mechanism of low-frequency sonophoresis [32]. Application of low-frequency ultrasound produces cavitation, which in turn disorders lipid bilayers of the skin. This leads to the formation of aqueous channels in the skin [28]. Current-carrying ions as well as drugs can permeate through these channels. Therefore, the transport pathways for the drugs during low-frequency sonophoresis are the same as those for the current-carrying ions. Hence, the correlation between skin conductivity and skin permeability is fundamentally understandable. Quantitative aspects of this correlation are discussed elsewhere [32].

The increase in skin conductivity varies with the total energy, E, of ultrasound ($E = I\delta$, where I is ultrasound intensity (W/cm^2) and δ is the net exposure time (seconds) delivered to the skin. There exists a threshold of ultrasound energy, $E_{\text{threshold}}$, below which no significant change in the electrical conductivity of skin is observed. For rat skin (in vivo), this threshold is about 10 J/cm^2 [20]. After application of an ultrasound dose of 1000 J/cm^2, the skin conductivity showed an enhancement of 60-fold over the conductivity of untreated skin. The threshold energy for enhancement in pig skin was about 10 times higher compared to rat

Copyright © 2003 Marcel Dekker, Inc.

skin [20]. The threshold energy required for conductivity enhancement can be reduced by about 10-fold by combining low-frequency ultrasound with chemical enhancers such as surfactants, for example, 1% w/v sodium lauryl sulfate [33].

Skin remained in a state of elevated conductivity for prolonged times. Note that the skin permeability would eventually recover to its baseline value. For example, experiments on type I diabetic volunteers have shown that a 2-min application of ultrasound (20 kHz, ~7 W/cm^2) significantly increased skin permeability for about 15 h, after which skin permeability decreased to its baseline permeability within 24 h [34].

Effect of ultrasound pretreatment on macromolecule transport was assessed in vivo using rats for two molecules, low-molecular-weight heparin (LMWH) and insulin. Transdermal LMWH delivery was measured by monitoring aXa activity in the blood while transdermal insulin delivery was monitored using blood glucose values. No significant aXa activity was observed when LMWH was placed on nontreated skin. However, a significant amount of LMWH was transported transdermally after ultrasound pretreatment. aXa activity in the blood increased slowly for about 2 h, after which it increased rapidly before achieving a steady state after 4 h at a value of about 1 U/mL [30]. Effect of transdermally delivered LMWH was observed well beyond 6 h, in contrast to intravenous or subcutaneous injections, which resulted in only transient biological activity.

Effect of ultrasound on transdermal insulin delivery was also measured. In these experiments, skin was permeabilized using low-frequency ultrasound (20 kHz, ~7 W/cm^2). Insulin (500 U/mL) was placed on permeabilized skin. Blood glucose levels were subsequently measured. Blood glucose level of rats decreased by about 80% when insulin was applied on an ultrasound-treated site, thus suggesting that a significant dose of insulin was delivered across the skin. In contrast, no effect on blood glucose level was observed when insulin was placed on an untreated site.

The delivery rate of drugs can be further enhanced by providing additional driving forces (additional ultrasound or iontophoresis) that may induce convection through ultrasound-pretreated skin. For example, application of low-intensity ultrasound (~1 W/cm^2) on ultrasonically pretreated skin induced an additional 21-fold enhancement of transdermal mannitol transport compared to that due to pretreatment alone [29]. The enhancement induced by additional ultrasound decreased immediately after the ultrasound was turned off. Application of iontophoresis also induced additional enhancement across ultrasound-pretreated skin. Specifically, transdermal heparin transport after 1 h of iontophoresis across ultrasound pretreated skin was 15-fold higher compared to that induced by ultrasound alone [24].

Enhanced skin permeability by ultrasound application may be used for delivery of various therapeutic agents. With a typical permeability achieved after ultrasound pretreatment, an insulin dose of about 1 U/h can be delivered through

Copyright © 2003 Marcel Dekker, Inc.

a patch having an area of 10 cm^2 and containing insulin solution at a concentration of 100 U/mL. This dose is comparable to a typical baseline insulin dose for a type I diabetic patient [16]. This dose can be further increased by providing additional application of low-intensity ultrasound. Sonophoretic drug delivery methods can also be used for several other drugs, including leutinizing hormone releasing hormone (LHRH). Further work in this area should focus on optimization of ultrasound parameters for increasing the delivery rates, performing detailed safety studies, and tests on human volunteers.

Low-frequency sonophoresis also has applications in diagnostics. Specifically, a sample of interstitial fluid can be extracted through ultrasonically pretreated skin for diagnostic purposes [34]. This method has been tested in vitro and in vivo in animals as well as in human volunteers. Using rat as an animal model, it was shown that low-frequency ultrasound (20 kHz, ~7 W/cm^2) can quickly permeabilize skin. Glucose was extracted through the sonicated site using vacuum (10 in Hg). The first extraction flux was used for calibration and subsequent fluxes were used for prediction of blood glucose levels. The relationship

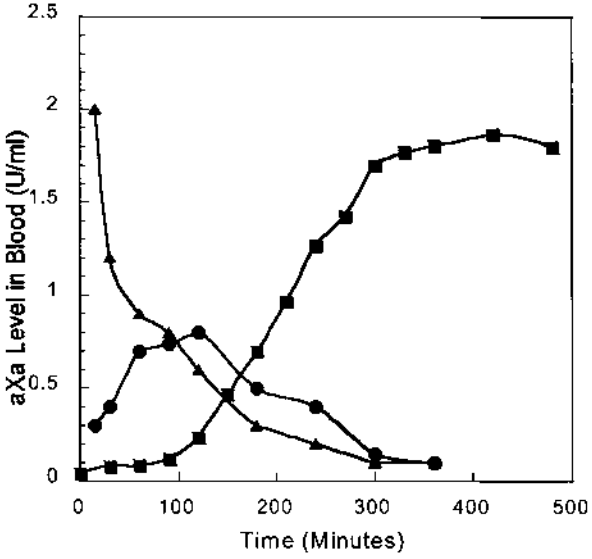


Figure 1 Comparison of aXa profiles in the blood after transdermal delivery (closed squares) with a single subcutaneous injection (closed circles, 150 U/kg) and intravenous injection (closed triangles, 150 U/kg) in rats. For transdermal delivery, the skin was permeabilized with ultrasound and 150 U/mL of low-molecular-weight heparin was placed on the skin (from Ref. [30]). Data for injections taken from Ref. [35].

Copyright © 2003 Marcel Dekker, Inc.

between reference glucose levels and sonophoretically predicted glucose levels was excellent (mean relative error of 17%) [34]. This method was also tested on type I diabetic human volunteers. Once again, the correlation between predicted and measured glucose values was excellent (mean relative error of 23%). Similar strategies may be used to noninvasively measure other analytes including electrolytes and blood gas. Initial safety studies indicated that ultrasound did not induce adverse effects on the skin. Specifically, no damage or irritation was observed by visual inspection. Further studies in this area should focus on conducting detailed safety studies and sensor development.

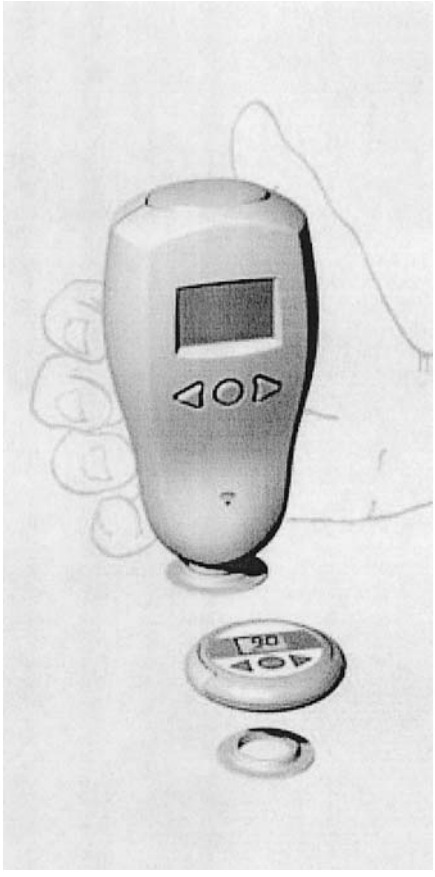


Figure 2 A schematic of how a low-frequency sonophoresis device may be used for skin permeabilization followed by glucose extraction or drug delivery. (From Ref. [34].)

Copyright © 2003 Marcel Dekker, Inc.

V. TECHNOLOGY POSITION AND FUTURE DIRECTIONS

Low-frequency sonophoresis offers an effective method for enhancing skin permeability (Fig. 1). Enhanced skin permeability may be used for the purpose of drug delivery as well as diagnostics. Therapeutic doses of drugs such as insulin can be delivered through permeabilized skin. Enhanced skin permeability may also be used to extract glucose across the skin. Extracted glucose may be measured and used to predict blood glucose levels. These two methods may someday be combined to develop self-regulated closed-loop delivery devices for drugs such as insulin (Fig. 2). Such devices may noninvasively deliver and monitor drugs (such as insulin) and maintain the desired drug concentration in the body.

Several other strategies including the use of chemicals [36,37] and electric fields [38,39] have been suggested for noninvasive transdermal drug delivery and/or diagnostics. Low-frequency sonophoresis offers advantages method compared to these methods in that the enhancements are high and applicable to a wide variety of molecules (hydrophilic/lipophilic, charged/uncharged, high/low molecular weight). At the same time, this method requires a more sophisticated device compared to other methods. Additional research and development is necessary before low-frequency sonophoresis can be applied in clinical practice. Specifically, attention should be focused on device development and safety assessment.

REFERENCES

1. RL Bronaugh, HIE Maibach, eds. Percutaneous Absorption: Mechanisms—Methodology—Drug Delivery. New York: Marcel Dekker, 1989.
2. M Prausnitz. Reversible skin permeabilization for transdermal delivery of macromolecules. Crit Rev Ther Drug Carr Syst 14:455–483, 1997.
3. J Kost. Ultrasound for controlled delivery of therapeutics. Clin Mater 13:155–161, 1993.
4. K Tachibana. Transdermal delivery of insulin to alloxan-diabetic rabbits by ultrasound exposure. Pharm Res 9:952–954, 1992.
5. EJ Novak. Experimental transmission of lidocaine through intact skin by ultrasound. Arch Phys Med Rehab 5(May):231–232, 1964.
6. BM Cameroy. Ultrasound enhanced local anesthesia. Am J Orthoped 8:47, 1966.
7. HAE Benson, JC McElnay, R Harland. Use of ultrasound to enhance percutaneous absorption of benzydamine. Phys Ther 69:113–118, 1989.
8. HAE Benson, JC McElnay, J Hadgraft. Influence of ultrasound on the percutaneous absorption of nicotinate esters. Pharm Res 9:1279–1283, 1991.
9. D Bommannan, GK Menon, H Okuyama, PM Elias, RH Guy. Sonophoresis. II. Examination of the mechanism(s) of ultrasound-enhanced transdermal drug delivery. Pharm Res 9:1043–1047, 1992.

Copyright © 2003 Marcel Dekker, Inc.

10. CD Ciccone, BQ Leggin, JJ Callamaro. Effects of ultrasound and trolamine salicylate phonophoresis on delayed-onset muscle soreness. Phys Ther 71:666–678, 1991.
11. JE Griffin, JL Echternach, RE Proce, C Touchstone. Patients treated with ultrasonic driven hydrocortisone and with ultrasound alone. Phys Ther 47:600–601, 1967.
12. ME Johnson, S Mitragotri, A Patel, D Blankschtein, R Langer. Synergistic effect of ultrasound and chemical enhancers on transdermal drug delivery. J Pharm Sci 85:670–679, 1996.
13. D Levy, J Kost, Y Meshulam, R Langer. Effect of ultrasound on transdermal drug delivery to rats and guinea pigs. J Clin Invest 83:2074–2078, 1989.
14. JC McElnay, MP Matthews, R Harland, DF McCafferty. The effect of ultrasound on the percutaneous absorption of lignocaine. Br J Clin Pharmacol 20:421–424, 1985.
15. JC McElnay, TA Kennedy, R Harland. The influence of ultrasound on the percutaneous absorption of fluocinolone acetonide. Int J Pharm 40:105–110, 1987.
16. S Mitragotri, D Blankschtein, R Langer. Ultrasound-mediated transdermal protein delivery. Science 269:850–853, 1995.
17. AJ Mortimer, BJ Trollope, OZ Roy. Ultrasound-enhanced diffusion through isolated frog skin. Ultrasonics 26:348–351, 1988.
18. K Tachibana, S Tachibana. Use of ultrasound to enhance the local anesthetic effect of topically applied aqueous lidocaine. Anesthesiology 78:1091–1096, 1993.
19. J Kost, D Levy, R Langer. Ultrasound as a transdermal enhancer. In R Bronaugh, HI Maibach, eds. Percutaneous Absorption: Mechanisms—Methodology—Drug Delivery. New York: Marcel Dekker, 1989, pp. 595–601.
20. S Mitragotri, M Coleman, J Kost, R Langer. Transdermal analyte extraction using low-frequency ultrasound. Pharm Res 17:466–470, 2000.
21. S Mitragotri, J Farrell, H Tang, T Terahara, J Kost, R Langer. Determination of the threshold energy dose for ultrasound-induced transdermal drug delivery. J Control Rel 63:41–52, 2000.
22. S Mitragotri, D Blankschtein, R Langer. Sonophoresis: Enhanced transdermal drug delivery by application of ultrasound. In: J Swarbrick, J Boylan, eds. Encylopedia of Pharmaceutical Technology. NY: Marcel Dekker, 1996, pp. 103–122.
23. S Mitragotri, R Langer, J Kost. Ultrasound for modulation of skin properties. In: D Wise, ed. Biomaterials Engineering and Devices: Human Applications. Totowa, NJ: Humana Press, 1999, pp. 843–854.
24. L Le, J Kost, S Mitragotri. Synergistic effect of ultrasound and iontophoresis on transdermal drug delivery: applications to heparin delivery. Pharm Res 17:1151–1154, 2000.
25. S Mitragotri, D Ray, J Farrell, H Tang, B Yu, J Kost, D Blankschtein, R Langer. Enhancement of transdermal transport using ultrasound and surfactants. Proc Int Symp Control Rel Bioact Mater 26:176–177, 1999.
26. K Fellinger, J Schmidt. Klinik Therapies des Chromischen Gelenkreumatismus. Vienna, Austria: Maudrich, 1954, pp. 549–552.
27. S Mitragotri, D Blankschtein, R Langer. An explanation for the variation of the sonophoretic transdermal transport enhancement from drug to drug. J Pharm Sci 86: 1190–1192, 1997.

Copyright © 2003 Marcel Dekker, Inc.

28. S Mitragotri, D Blankschtein, R Langer. Transdermal drug delivery using low-frequency sonophoresis. Pharm Res 13:411–420, 1996.
29. W Gaertner. Frequency dependence of acoustic cavitation. J Acoust Soc Am 26: 977–980, 1954.
30. S Mitragotri, J Kost. Transdermal delivery of heparin and low-molecular weight heparin. Pharm Res. In press.
31. S Mitragotri, J Kost. Low-frequency sonophoresis: a non-invasive method for drug delivery and diagnostics. Biotech Progress 16:488–492, 2000.
32. H Tang, S Mitragotri, D Blankschtein, R Langer. Theoretical description of transdermal transport of hydrophilic permeants: application to low-frequency sonophoresis. J Pharm Sci 90:543–566, 2001.
33. S Mitragotri, D Ray, J Farrell, H Tang, B Yu, J Kost, D Blankschtein, R Langer. Synergistic effect of ultrasound and sodium lauryl sulfate on transdermal drug delivery. J Pharm Sci 89:892–900, 2000.
34. J Kost, S Mitragotri, R Gabbay, M Pishko, R Langer. Transdermal extraction of glucose and other analytes using ultrasound. Nat Med 6:347–350, 2000.
35. L Piazolo, J Harenberg, R Malsch, FG Huttner, DL Heene. Comparison of the pharmacodynamic and pharmacokinetic profiles of two low molecular-weight-mass heparins in rats. Semin Thromb Hemost 23:109–117, 1997.
36. CA Phillips, BB Michniak. Transdermal delivery of drugs with differing lipophilicities using Azone analogs as dermal penetration enhancers. J Pharm Sci 84:1427–1433, 1995.
37. KA Walters. Penetration enhancers and their use in transdermal therapeutic systems. In: J Hadgraft, RH Guy, eds. Transdermal Drug Delivery: Developmental Issues and Research Initiatives. New York: Marcel Dekker, 1989, pp. 197–233.
38. RH Guy, Y Kalia, M Delgado-Charro, V Merino, A Lopez, D Marro. Iontophoresis: electrorepulsion and electroosmosis. J Control Rel 64:129–132, 2000.
39. MR Prausnitz, V Bose, R Langer, JC Weaver. Electroporation of mammalian skin: a mechanism to enhance transdermal drug delivery. Proc Natl Acad Sci USA 90: 10504–10508, 1993.

Copyright © 2003 Marcel Dekker, Inc.

47

SLN and Lipopearls for Topical Delivery of Active Compounds and Controlled Release

Rainer Helmut Müller and Sylvia Andrea Wissing
Free University of Berlin, Berlin, Germany

I. INTRODUCTION

At the beginning of the 1990s, solid lipid nanoparticles (SLN®) manufactured from polymers and macromolecules were developed as an alternative carrier system to emulsions, liposomes, and nanoparticles. The matrix of SLN comprises solid lipids, and in general, they are produced by high-pressure homogenization [1–3]. An alternative production method is the microemulsion technique [4]. The features of SLN can be summarized in one sentence: they combine the advantages of traditional dosage forms such as emulsions, but simultaneously avoid some of the pronounced disadvantages associated with such systems.

SLN are composed of well-tolerated and regulatory-acceptable excipients that are identical to emulsions and liposomes. Similar to the other nanoparticles, they possess a solid matrix allowing controlled release and protection of incorporated active ingredients against degradation. SLN can be used in place of conventional dosage forms in various potential areas of application.

At the beginning, SLN were developed primarily for intravenous administration; then, as they developed further, SLN were exploited for oral drug delivery, e.g., of cyclosporine [5]. Beginning about 4 years ago, attention focused on the use of SLN in topical formulations with not only pharmaceutical, but also cosmetic, applications. Worldwide-registered tradenames are SLN®* and, for topical products, Lipopearls®*.

* Trademarks by SkyePharma PLC.

Copyright © 2003 Marcel Dekker, Inc.

The SLN patent was submitted as a German application in 1991 (priority date November 1991); then a PCT application was filed and subsequently patents have been granted in most countries, e.g., Ref. [1]. Therefore, one of the important prerequisites for the introduction of a product into the market—exclusiveness—has been met. Other important prerequisites for the market, such as low-cost production and the possibility of large-scale production, are also fulfilled with this technology.

For topical application, various very different active ingredients have been incorporated in SLN, including drugs, e.g., prednisolone [6,7], cosmetic compounds such as retinol [8] and coenzyme Q10 [9], sunscreens [10], and perfumes [11]. SLN have been incorporated into o/w creams and gels and their interaction with these bases has been studied. These studies included physical stability, and particles have been optimized and characterized with respect to drug loading and release properties. This chapter reviews the achieved state of the art of SLN and Lipopearls.

II. HISTORICAL DEVELOPMENT

A. Limitations of Existing Technologies

SLN were developed to overcome some of the limitations associated with other available dosage forms such as emulsions, liposomes, and nanoparticles; o/w emulsions can serve as carriers for poorly water-soluble drugs. Diazepam, etomidate, and propofol are examples of o/w emulsion formulations that are on the market. However, despite the good tolerability of these emulsions, the number of products on the market remains limited [12]. The reason for this is that many oils, especially regulatory-accepted oils, exhibit a poor capacity for solubilization of most drugs of interest for commercialization; i.e., they have insufficient loading capacity. Liposomes have been extensively investigated as a platform for drug delivery; however, the problems associated with liposomes include physical stability and, most important, the relatively high price of the products. For example, physicians are reluctant to use the liposomal amphothericin product Ambisome® because of its price. Indeed, sometimes even admixtures of amphothericin solutions are used as a cheap replacement to the Ambisome product even though there is the potential for precipitation of the amphotericin. The number of liposomal products is increasing, but currently no "cheap" liposome is available, thereby restricting the broad use of this carrier system. Nanoparticles have also been examined for their potential as drug delivery systems. However, a clear disadvantage of nanoparticles is the lack of suitable large-scale production methods leading to a product that is acceptable by the regulatory authorities and simultaneously cost-effective. The aim was therefore to develop a carrier system having a better performance regarding these limitations and problems.

Copyright © 2003 Marcel Dekker, Inc.

B. Historical Application of Large Lipid Particles

For many years, large lipid particles have been used in the form of pellets for oral drug delivery, e.g., the product Mucosolvan® by Boehringer Ingelheim (Germany). Lipid microparticles and their manufacturing techniques have also been described, e.g., lipid microparticles produced by spray congealing [13]. The next development phase for large lipid particles was the production of lipid nanoparticles for oral delivery by Speiser [14]. Melted lipids were dispersed by stirring or sonication in an aqueous surfactant solution. A similar system was the lipospheres described by Domb [15]. However, the disadvantage of using low-energy dispersion techniques was the need for relatively high surfactant concentrations to obtain an ultrafine nanoparticulate product. An additional problem was the requirement to reduce the microparticle content of the final product. This was especially important for products designed for intravenous administration. A possible solution to this was a self-emulsifying system that used high surfactant concentrations, but again, this was of little or no use for an intravenous product, because often a mixture of nanoparticles and microparticles was obtained [2].

C. High-Pressure Homogenization

To obtain a homogeneous product with small particle size and minimal content of microparticles, a high-pressure homogenization method was developed. Highly concentrated lipid nanoparticle dispersions (e.g., 20–30%) can be obtained using a low stabilizer/surfactant concentration (e.g., approximately 1%), being of a quality even suitable for intravenous injection.

III. DESCRIPTION OF TECHNOLOGY

A. Laboratory-Scale Production

For incorporation of the drug into the lipid, the drug is dissolved, solubilized, or dispersed in the melted lipid (approximately 5–10°C above melting point); then the lipid melt is dispersed in an aqueous surfactant solution by stirring to obtain a pre-emulsion. This preemulsion is homogenized above the melting point using a piston-gap homogenizer, e.g., Micron Lab 40 (APV Deutschland GmbH, Germany). Typical production parameters for the hot homogenization technique are 500 bar, three homogenization cycles, 60–90°C. In the case of hydrophilic drugs, these drugs would partition into the water phase when using the hot homogenization technique. Therefore, a cold homogenization technique would be applied.

The resultant drug-containing melt is solidified and milled to obtain lipid microparticles. These microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. This suspension is then homogenized as described

Copyright © 2003 Marcel Dekker, Inc.

above but at room temperature or below, and the microparticles disintegrate directly into solid lipid nanoparticles. Details of the production method have been described [1,16,17].

B. Production of Clinical Batches

The availability of a qualified, approved production unit for clinical batches is a prerequisite to perform a clinical study. To obtain a sufficiently large batch size for a clinical study, a Micron Lab 60 was slightly modified (addition of large product containers, double-walled tubes with temperature control, electropolished surfaces, etc.) [17]. In the continuous, circulating mode, a batch of 2-kg dispersion can be produced within 15 min; in the discontinuous mode a batch of 10 kg can be produced within 20 min. Owing to the improved dispersion efficiency of the Lab 60 (two homogenization valves) compared to the Lab 40 (one valve), a lower homogenization pressure of 200 bar for the first valve and 50 bar for the second valve can be used. In the discontinuous mode, generally only two homogenization cycles are required compared to three when using the Lab 40. In addition, often the sizes are smaller and the width of distribution is narrower as well. That means, in contrast to many other processes during scaling up, SLN production at larger scale is easier and yields an even higher-quality product compared to laboratory scale.

C. Large-Scale Production

For highly potent drugs, the capacity of the Lab 60 is already sufficient to produce an industrial batch [e.g., interferon, erythropoietin (EPO)]. When producing 100 kg or a ton of SLN dispersion, passing the dispersion a second time through the same homogenizer (second homogenization cycle) exposed the product to an elevated temperature for a longer time. Therefore, a production line was developed placing two homogenizers in series. For the second homogenization cycle, the product passes the second homogenizer; then it can be cooled down immediately in a controlled way [17]. By using static blenders, the different compounds for the SLN dispersion can be mixed just before entering the first homogenizer, further reducing the temperature load.

IV. DRUG INCORPORATION AND RELEASE

A. Drug Incorporation

The drug-loading capacity of SLN, calculated in percent of particle mass (lipid + drug), depends on the lipophilicity of the drugs and the chemical nature of the lipid matrix. For example, for the lipophilic peptide cyclosporine, a loading ca-

Copyright © 2003 Marcel Dekker, Inc.

pacity of 20% was obtained in SLN made from Imwitor 900. For coenzyme Q10, particles were produced with a 26% loading capacity [18]. However, for compounds such as Q10, since they are miscible with lipids without miscibility gap, loading capacities of 50% and more can be achieved. However, if there is too little matrix material, controlled-release properties will be lost. Incorporation of hydrophilic drugs is much more limited, for example, for the highly water-soluble model drug iotrolan a drug loading of 0.5% was reported [19]. However, this percentage is sufficient for highly potent drugs such as EPO.

During the cold homogenization stage, the microparticles are disintegrated and new surfaces form, leading to a large increase in the total surface area of the particles. Hydrophilic drugs at the surface become dissolved into the dispersion medium. This results in a reduction of the entrapment efficiency for hydrophilic drugs. To avoid this, SLN can be produced by replacing the dispersion medium, water, with a nonaqueous medium having low solubility for the hydrophilic drug, e.g., oils such as Miglyol or liquid polyethylene glycol (PEG) 400 or 600. An advantage of using liquid PEG is that it yields an SLN dispersion that is suitable for direct filling of soft gelatin capsules.

The nature of the lipid matrix (i.e., the solubility of the drug in the lipid and the structure of the lipid) also affects drug loading. To find a suitable lipid matrix material, lipids need to be screened for their dissolution capacities for the specific drug. It should be kept in mind that the solubility of the drug in the melted lipid is higher than in the solid lipid. If the drug concentration in the SLN dispersion is above its saturation solubility in the solid lipid, the drug will be expelled from the particles during the cooling and solidification process after the hot homogenization phase, resulting in drug crystals being observed in the SLN dispersion.

Related to solubility is, of course, the crystalline structure of the lipid forming the SLN. Chemically uniform lipids forming a highly crystalline, perfectly ordered structure with no imperfections will expel the drug (e.g., SLN made from chemically pure tripalmitin [20,21]). Chemically polydisperse lipids, e.g., mixtures of mono-, di-, and triglycerides composed of fatty acids with very different lengths including unsaturated fatty acids, form crystals with many imperfections. As a result the drug molecules can be accommodated between fatty acid chains, lipid lamella, and in amorphous clusters.

B. Drug Release

Since the degree of order increases and the number of imperfections decreases when transforming from α- to β′/βi- and finally to the β-modification, the particles produced should preferably not show a too large fraction of the stable β-modification. Conversely, reduced solubility of the drug in the β-modification can be exploited for triggered drug release, e.g., retinol SLN for dermal delivery

Copyright © 2003 Marcel Dekker, Inc.

[22,23]. Triggered by water evaporation and temperature increase after application to the skin, the particles transform to a β-modification, drug solubility is reduced, and the drug is released (see below).

In the literature, three different models for drug incorporation and consequently different release patterns are described [3]:

Model 1. Lipid core, drug-enriched shell
Model 2. Solid solution
Model 3. Drug-enriched core, lipid shell (membrane)

A recent addition to this list is:

Model 4. Nanocompartment particles [22,23]

By fine tuning of the production parameters a desired percentage of drug can be localized and enriched in the outer shell of the particles. This fraction of the drug in the shell will be released in a burst, serving as initial dose. The production parameters that are varied to modify the percentage of drug localized in the outer shell are surfactant concentration and production temperature. The two extremes that can be obtained by varying these production parameters are models 1 and 2. At the one extreme, complete localization of the drug in the outer shell leads to a complete release as a burst within a few minutes, whereas at the other extreme, an even distribution of the drug as a solid solution throughout the particle is achieved that leads to a prolonged release profile. For prednisolone SLN, a prolonged release in vitro for up to 6 weeks has been described [24]. To obtain model 3, the drug needs to first crystallize during the cooling process within the hot homogenization technique. These three models have been previously discussed in detail [3].

Recently SLN containing nanocompartment particles have been described (model 4). As discussed above, it is preferred to use chemically polydisperse lipids instead of using one homogeneous lipid. The polydispersity will be even higher when mixing different solid lipids, i.e., lipid blends. It was found that if, instead of blending solid lipids, the solid lipid was blended with liquid lipids (oils), an improvement in drug loading could be achieved. For example, this approach improved the drug loading for retinol from 1% in Compritol to approximately 6% in a Compritol/Miglyol matrix. Retinol itself is soluble in Miglyol; indeed a stabilized Miglyol solution with retinol is on the market (Retinol® 10CM, BASF). In general, the drug loading of retinol increased with increasing fraction of Miglyol in the lipid blend. At low Miglyol fraction in the lipid blend, the improved loading could be explained by distortion of the lipid structure and creation of imperfections. However, with higher Miglyol fractions in the blend, liquid Miglyol nanocompartments were formed, leading to model 4. The solubility of retinol in the liquid Miglyol is higher than in the solid Compritol, thus leading to a higher drug loading due to the presence of Miglyol nanocompartments within

Copyright © 2003 Marcel Dekker, Inc.

the SLN. The presence of liquid Miglyol and its existence in nanocompartment form was proven by DSC [22], and the association of the liquid oil with the solid lipid particles by ESR measurements [25]. The release of drugs from this type of SLN involves both diffusion from the oily nanocompartments through the solid lipid matrix and simultaneous release of drug that is dissolved in the solid lipid matrix.

V. TOPICAL SYSTEMS BASED ON SLN

A. Loading of Creams and Gels with SLN

1. Creams

SLN can be incorporated not only into simple o/w and w/o emulsions but also into multiple emulsions.

There are two different ways of incorporating SLN into creams: (a) the cream is produced with a reduced water content and a highly concentrated SLN dispersion is admixed to the cream; and (b) a part of the water phase of the cream is replaced by highly concentrated SLN dispersion; then the usual production method for the cream is applied.

In creams, the majority of SLN remains in the water phase, with only partial association to the surface of oil droplets being observed [27]. However, there was no dissolution of the SLN into the oil phase of the creams as shown by DSC measurements. The melting enthalpy of SLN in the cream remained unchanged during storage [16].

SLN have proved to be physically stable in creams, even when they are added to the water phase prior to the production of the cream [26].

2. Gels

To produce gels, a highly concentrated SLN dispersion can be admixed to a gel with reduced water content. Alternatively, the gel-forming excipient (e.g., cellulose ethers, xanthan gum, polyacrylates, etc.) can be added to the SLN dispersion containing all ingredients of the final gel formulation.

3. Improved Methods: One-Step-Production of Topical SLN Creams

Admixing of SLN to creams or replacing a part of the water phase limits the total amount of SLN that can be incorporated in such a cream. For example, replacing 30% of such a cream formulation by a 20% aqueous SLN dispersion will lead to a final concentration of about 6.6% of particles in the cream. This

Copyright © 2003 Marcel Dekker, Inc.

might not be sufficiently high to incorporate the desired amount of active ingredient or to achieve an occlusive effect.

Recently, lipid particle dispersions with a lipid content of 40% were produced by high-pressure homogenization. The product had a cream-like consistency without having the bicoherent or tricoherent structure of an ointment. The existence of intact, definite lipid nanoparticles could be proven. At a concentration of 40% solid, these nanoparticles form a gel network with viscoelastic properties of a typical cream. The particles were observed to form a pearl network that has been described for Aerosil gels. The particulate character of the particles also remains unchanged during storage [28–30]. The structure of these new parti-

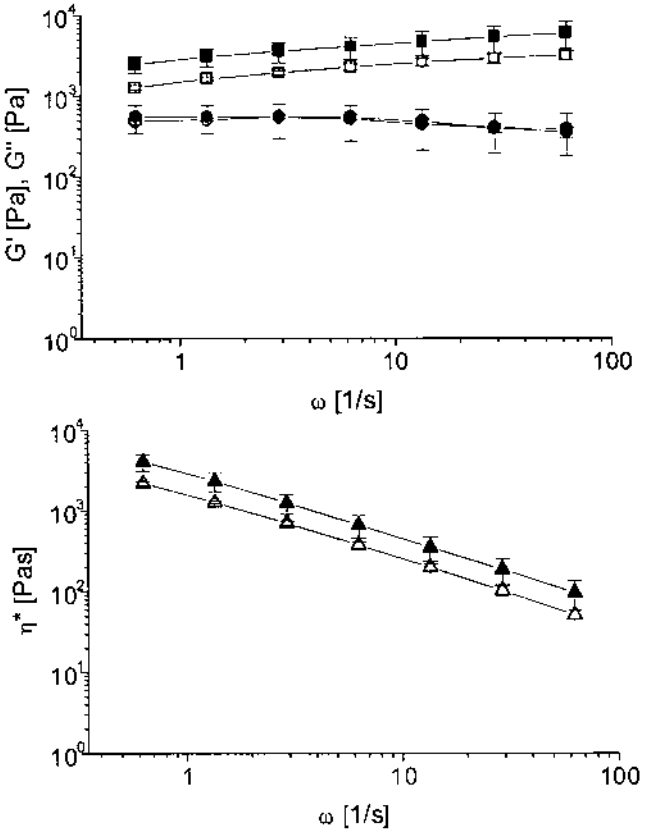


Figure 1 (Top) Storage modulus G′ (■ for SLN, □ for cream) and loss modulus G″ (● for SLN, ○ for cream) of SLN and classical cream. (Bottom) Complex viscosity η* of SLN and classical cream (▲ for SLN, △ for cream). (Modified from Ref. [30].)

Copyright © 2003 Marcel Dekker, Inc.

cle gels was investigated using oscillatory measurements. Loss modulus, elastic modulus, and viscosity were found comparable to the classical cream unguentum emulsificans aquosum (DAB) (Fig. 1) [28].

B. Properties of SLN Formulations

1. Occlusive Effect of SLN

It has been reported that SLN lead to an occlusive effect [9,16,18,31]. An in vitro model has been used to quantify the occlusive effect. Beakers with water were covered with a filter. An SLN formulation or, for comparison purposes, other formulations were spread on the filter and the water evaporation through the filter was compared to the control (filter only). An occlusivity factor was calculated being 0 for no effect and 100 for prevention of any water evaporation at all. Comparing SLN dispersions with lipid microparticle dispersions (1 μm) at identical lipid concentrations revealed that there is only an occlusive effect when using SLN (Fig. 2). To investigate the increase in occlusivity, SLN were admixed to a cream, which led to a distinct increase in the occlusion. It should be realized that SLN cannot increase the occlusivity of an ointment since it already possesses a highly occlusive nature, i.e., an occlusion factor of 80–100 (e.g., petrolatum). In other words, therefore, the advantage of SLN is that they increase the occlusivity of an o/w cream without leading to the glossy appearance of highly occlusive creams (i.e., the w/o type) or greasy nature of ointments.

The occlusion effect appears to be dependent on particle size, lipid concen-

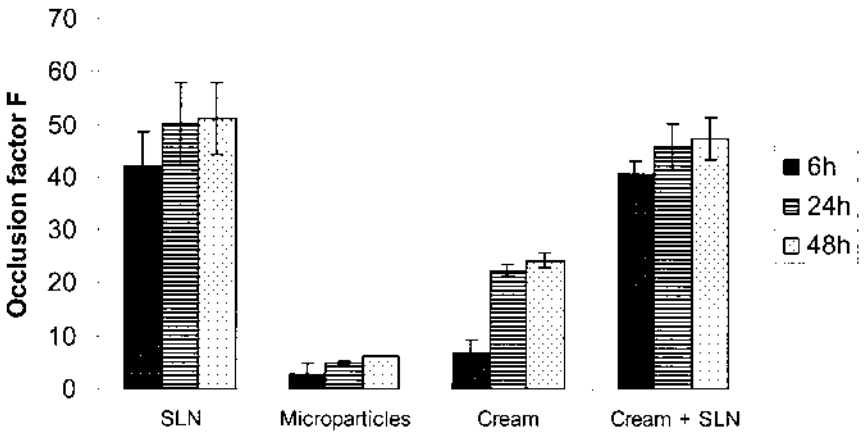


Figure 2 Occlusion factor (F) of SLN, microparticles, classical cream, and SLN admixed to classical cream after 6, 24, and 48 h. (Modified from Ref. [18].)

Copyright © 2003 Marcel Dekker, Inc.

tration, and nature of the lipid. The explanation for the occlusion effect is the formation of a densely packed film. The pores between lipid microparticles are relatively large; however, between lipid nanoparticles they are very small, and because the dimensions are hydrodynamically unfavorable for water evaporation, an occlusive effect occurs. Recent electron microscopic data suggested that there was the formation of a dense film without pores (similar to film formation when coating tablets with aqueous nanoparticulate polymer dispersions, e.g., Eudragit).

It should be noted that there are some contradictory results from in vivo studies regarding the occlusive effect. As mentioned above, the degree of occlusiveness obviously depends on various factors and needs to be optimized on a case-by-case basis. Occlusion below the expected values might therefore be explained as due to a suboptimal composition of the SLN system.

At present, detailed investigations are being performed to determine the conditions for maximal occlusion. Studies on skin hydration and skin microtopography have shown an increased skin hydration and a more pronounced wrinkle-smoothing effect compared to the commercial product tested as reference. In this study, SLN were admixed to the commercial product [3].

2. Drug Penetration into the Skin

Various active ingredients with interest for cosmetic products were incorporated into SLN, and their drug penetration into the skin was studied using the stripping test. Penetration was studied in humans by applying 20 mg of the formulations at room temperature and 62% relative humidity on an area of 4 cm^2 on the lower left arm. Tocopherol and tocopherol acetate were applied to the skin as an aqueous SLN dispersion; the reference formulations were ethanolic solutions. After 30 min of incubation, the skin was washed and nine strippings were taken. The drug was extracted with 2 mL of solvent and quantitatively analyzed using HPLC. Plotting the accumulative amount of drug penetrated showed higher values for the SLN formulations (Fig. 3). In another study higher penetration was also observed for coenzyme Q10 compared to solutions in isopropanol and paraffin.

Intensive in vitro penetration studies have been performed using pig skin in a Franz cell [8]. The reference—retinol in o/w emulsion—released the drug with a constant rate (approximately 4.5), whereas an increasing rate of retinol release from SLN led to differences in the retinol concentrations as a function of skin layer and time.

3. Triggered Drug Release from Topical Lipid Particles

In vitro drug release from SLN occurs by diffusion, whereas in vivo drug release is also due to particle degradation by enzymes. The enzymatic contribution is much more pronounced for orally administered SLN than for topically applied particles.

Copyright © 2003 Marcel Dekker, Inc.

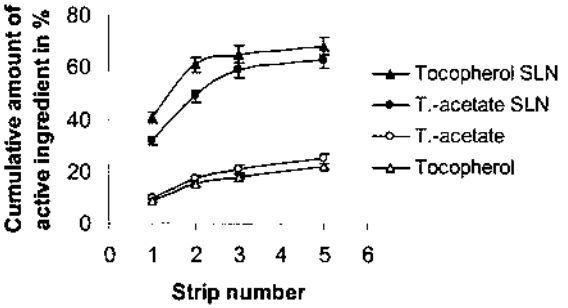


Figure 3 Penetration of tocopherol and tocopherol acetate formulations into the skin (SLN and ethanolic solution). (Modified from Ref. [18].)

To promote drug penetration, it would be desirable to have a high concentration of free drug in the topical formulation. This requires the fast release of drug from the SLN. Such a fast release requires that, in addition to drug diffusion, an additional release mechanism takes place i.e., controlled drug expulsion from the matrix. Such an expulsion can be obtained when the lipid transforms to the more stable modifications. For the developed product Retinol SLN, it can be shown that the lipids remain in α-/βi-modification during storage (Fig. 4). Application to the skin leads to water evaporation and temperature increase, which triggers the transformation into the stable β-modification (Fig. 4), consequently increasing release with progressing transformation (increasing packing density of lipid crystals).

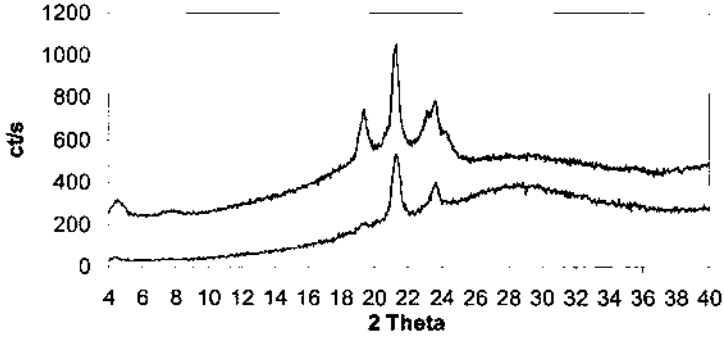


Figure 4 X-ray diffraction spectrum of retinol SLN before application to the skin (bottom) and spectrum taken 24 h after application to skin showing the transform to the stable modification due to water evaporation. (Modified from Ref. [23].)

Copyright © 2003 Marcel Dekker, Inc.

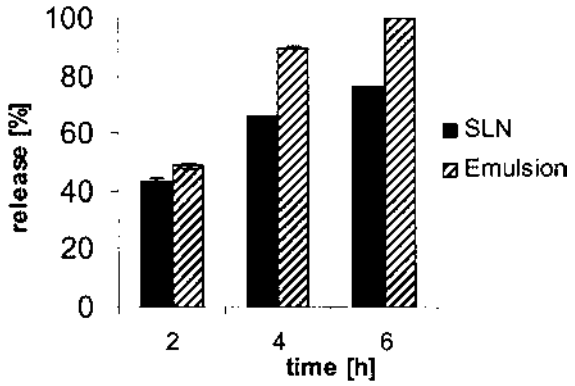


Figure 5 In vitro release of the perfume Allure of SLN and emulsion formulations. (Modified from Ref. [11].)

4. Prolonged Release of Perfumes and Fragrances

In contrast to accelerated release for enhancing drug penetration, for other compounds a very slow release is desirable. Examples include perfumes or fragrances in cosmetics or topical preparations. The perfume Allure was incorporated in SLN and in a reference o/w emulsion, and the in vitro release studied at 32°C. The SLN were able to retain the perfume more efficiently, thus prolonging its release (Fig. 5). The results of this study demonstrate the opportunity for the development of long-lasting perfumes on the basis of aqueous SLN dispersions, not only for cosmetic but also for pharmaceutical purposes.

For both applications there is a need for the aqueous SLN dispersions to be appropriate for application as a spray, e.g., in the pharmaceutical industry for the treatment of neurodermitis, since the use of a spray is more patient-friendly compared to a cream. In this respect it has been shown that aqueous SLN dispersions remain physically stable without aggregation during aerosolization. In the study SLN dispersions were nebulized with a Pariboy for pulmonary delivery [3]. The shear forces when passing the nozzle did not cause particle aggregation.

5. SLN as Sunscreens

Protecting the skin against ultraviolet (UV) radiation is an issue of increasing interest and importance. Molecular sunscreens can have side effects, e.g., penetration into the skin and irritancy [32,33]. As an alternative, particulate UV protectors such as titanium dioxide were used. However, there are suggestions in the literature that titanium dioxide can also penetrate into the skin [34]. Surprisingly, SLN were found to protect against UV radiation. In a study the effect was ob-

Copyright © 2003 Marcel Dekker, Inc.

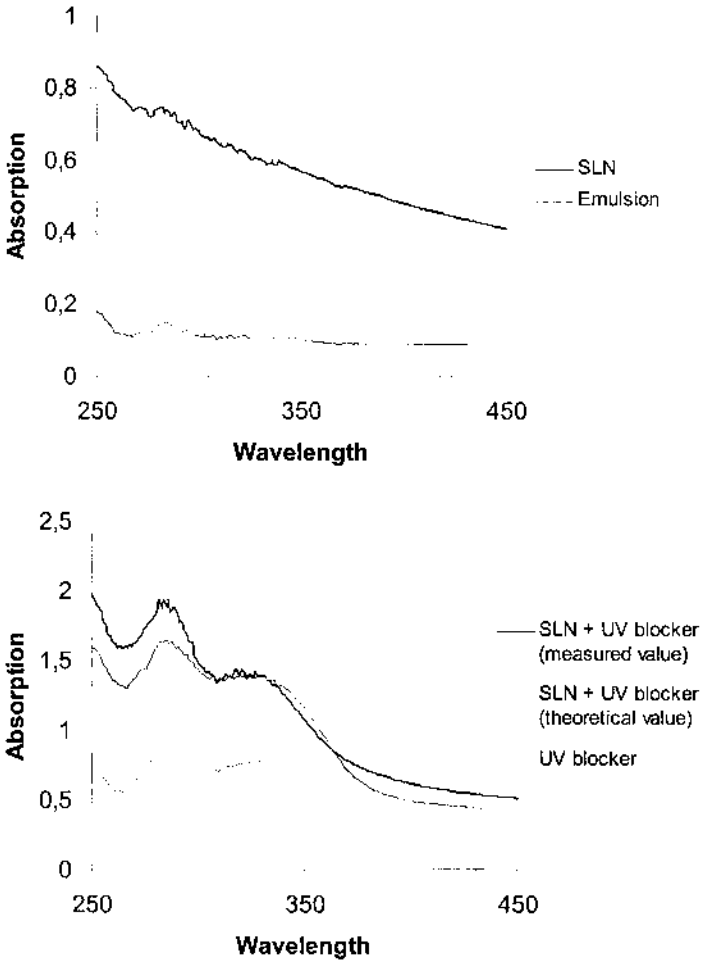


Figure 6 Wavelength scans from 450 to 250 nm showing absorption of SLN, o/w emulsion (top), UV blocker solution, theoretical effect of SLN combined with UV blocker, and measured effect thereof (bottom). (Modified from Ref. [10].)

served to be most pronounced when highly crystalline SLN were used. An o/w emulsion served as reference in this study (Fig. 6, top). Various molecular UV blockers were incorporated into SLN. In contrast to the incorporation of the sunscreens into the oil droplets of an emulsion, fixation of the molecules inside the SLN matrix minimized release and minimized penetration into the skin. The UV-blocking effect of the combination SLN + sunscreen was compared to the effect

Copyright © 2003 Marcel Dekker, Inc.

of each single compound. The combination appeared to be synergistic (Fig. 6, bottom). The results suggest that to achieve a low UV protection factor, it might be sufficient to produce a topical formulation with a high content of highly crystalline SLN. This avoids exposure to molecular sunscreens and potential side effects. If a higher protection factor is needed, SLN can be combined with molecular sunscreens. Owing to the synergistic effect, the total amount of molecular sunscreen can be reduced, thus reducing potential side effects.

VI. REGULATORY ISSUES

A regulatory prerequisite for the introduction of a formulation to the market is the acceptance of the excipients used. For the production of topically applied SLN, all excipients comprise those that are already accepted in cosmetic and pharmaceutical dermal formulations. This opens a broad choice of excipients, ranging from lipids to surfactants and stabilizers. Another regulatory requirement is that the production facilities need to be qualified and approved for the production of pharmaceuticals. The homogenizers used for the production of SLN are already used in the cosmetic and pharmaceutical industry. They are even used for the production of emulsions for intravenous infusion. Therefore, no regulatory problems regarding excipients and production lines are expected.

VII. TECHNOLOGY POSITION AND ITS COMPETITIVE ADVANTAGES

To judge the position of SLN technology, it needs to be compared to the competitive dosage forms currently available. These include o/w emulsions, liposomes, and nanoparticles made from polymers and macromolecules.

As seen from the low number of products on the market, the solubility of the regulatory accepted oils (e.g., MCT, LCT) is not sufficient for many drugs of interest. In addition, emulsions show very limited protection of incorporated drugs against chemical degradation owing to the permanent partitioning of drugs between the two liquid phases. The incorporation mechanism of drugs into SLN is different from emulsions (e.g., location in amorphous clusters), thus giving more flexibility with regard to drug incorporation. It has been shown that SLN protects incorporated drugs better than emulsions [23,35,36].

Many problems with liposomes have delayed their introduction to the cosmetic and pharmaceutical market (liposomes were first described by Bangham in 1968, the first cosmetic product Capture appeared in 1986, and the first pharmaceutical product around 1990). The number of pharmaceutical liposomal products is still low, owing mainly to problems such as stability. An additional drawback

Copyright © 2003 Marcel Dekker, Inc.

of liposomes are their production costs. A clear advantage of SLN is their cost-effectiveness due to low-cost excipients and low-cost production methods.

Nanoparticles made from polymers or macromolecules are not considered to be a competitive technology to SLN. Subsequent to their invention by Speiser, about 30 years of intensive research has not led to a significant number of products on the market. Apart from the costs associated with nanoparticle technology, from our point of view, the major obstacle is the lack of suitable and acceptable large-scale production methods.

VIII. FUTURE DIRECTIONS

SLN were invented at the beginning of the 1990s and are therefore a relatively young technology compared to emulsions, liposomes, and nanoparticles. However, since their introduction, a lot of basic research work has been performed to obtain a better understanding of the system, structure, and mechanisms. In parallel, the large-scale production technology has been developed and is advanced. The regulatory hurdles for the registration of topical products are relatively low, which should favor their fast introduction to the market. Meanwhile the technology has been moved from academia to industry; the drug delivery company SkyePharma PLC has acquired the worldwide rights and will further develop the technology. Therefore, the last requirement for a market introduction has been met, the availability of industrial development and production facilities.

REFERENCES

1. RH Müller, JS Lucks. Arzneistoffträger aus festen Lipidteilchen, Feste Lipidnanosphären (SLN). European patent 0605497, 1996.
2. RH Müller, W Mehnert, JS Lucks, C Schwarz, A zur Mühlen, H Weyhers, C Freitas, D Rühl. Solid lipid nanoparticles (SLN)—an alternative colloidal carrier system for controlled drug delivery. Eur J Pharm Biopharm 41:62–69, 1995.
3. RH Müller, K Mäder, S Gohla. Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. Eur J Pharm Biopharm 50:161–179, 2000.
4. MR Gasco. Method for producing solid lipid microspheres having a narrow size distribution. US patent 5,250,236, 1993.
5. RH Müller, SA Runge, V Ravelli. Pharmaceutical cyclosporin formulation of improved biopharmaceutical performance and improved physical quality and stability and process for producing same. German patent application, 1998.
6. A zur Mühlen, W Mehnert. Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles. Pharmazie 53:552, 1998.
7. W Mehnert, A zur Mühlen, A Dingler, H Weyhers, RH Müller. Solid Lipid Nanoparticles (SLN)—ein neuartiger Wirkstoff-Carrier für Kosmetika und Pharmazeutika.

Copyright © 2003 Marcel Dekker, Inc.

II. Wirkstoff-Inkorporation, Freisetzung und Sterilisierbarkeit. Pharm Ind 59(6): 511–514, 1997.
8. V Jenning, A Gysler, M Schäfer-Korting, S Gohla. Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug penetration into porcine skin. Eur J Pharm Biopharm 49:211–218, 2000.
9. B Siekmann, K Westesen. Preparation and physicochemical characterization of aqueous dispersions of coenzyme Q10 nanoparticles. Pharm Res 12:201–208, 1995.
10. SA Wissing, RH Müller. A novel sunscreen system based on tocopherol acetate incorporated into Solid Lipid Nanoparticles (SLN). Int J Cosm Sci 23:233–243, 2001.
11. SA Wissing, K Mäder, RH Müller. Solid lipid nanoparticles (SLN) as a novel carrier system offering prolonged release of the perfume Allure (Chanel). Proc Int Symp Control Rel Bioact Mater 27:311–312, 2000.
12. J Schmitt. Parenterale Fettemulsionen als Arzneistoffträger. In: RH Müller, GE Hildebrand, eds. Pharmazeutische Technologie: Moderne Arzneiformen, Stuttgart, Germany: WVGmbh, 1998, pp. 189–194.
13. T Eldem, P Speiser, A Hincal. Optimization of spray-dried and congealed lipid micropellets and characterisation of their surface morphology by scanning electron microscopy. Pharm Res 8:47–54, 1991.
14. P Speiser. Lipidnanopellets als trägersystem für arzneimittel zur peroralen anwendung. European patent EP 0167825, 1990.
15. A Domb. Lipospheres for controlled delivery of substances. US patent 5,188,837, 1993.
16. RH Müller A Dingler. The next generation after the liposomes: solid lipid nanoparticles (SLN, Lipopearls) as dermal carrier in cosmetics. Eurocosmetics 7/8:19–26, 1998.
17. RH Müller, S Gohla, A Dingler, T Schneppe. Large scale production of solid lipid nanoparticles (SLN) and nanosuspensions (DissoCubes). In: D Wise, ed. Handbook of Pharmaceutical Controlled Release Technology. 359–376, 2000.
18. A Dingler. Feste Lipid-Nanopartikel als kolloidale Wirkstoffrägersysteme zur dermalen Applikation. PhD thesis, Free University of Berlin, 1998.
19. H Weyhers. Feste Lipid Nanopartikel (SLN) für die gewebsspezifische Arzneistoffapplikation. PhD thesis, Free University of Berlin, 1995.
20. K Westesen, B Siekmann, MHJ Koch. Investigations on the physical state of lipid nanoparticles by synchroton radiation X-ray diffraction. Int J Pharm 93:189–199, 1993.
21. H Bunjes, K Westesen, MJH Koch. Crystallization tendency and polymorphic transitions in triglyceride nanoparticles. Int J Pharm 129:159–173, 1996.
22. V Jenning, AF Thünemann, SH Gohla. Characterisation of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. Int J Pharm 199:167–177, 2000.
23. V Jenning. Feste Lipid-Nanopartikel (SLN) als Trägersystem für die dermale Applikation von Retinol: Wirkstoffinkorporation,-freisetzung und Struktur. PhD thesis, Free University of Berlin, 1999.
24. A zur Mühlen, Feste Lipid Nanopartikel mit prolongierter Wirkstoffliberation—Herstellung, Langzeitstabilität, Cherakterisierung, Freisetzungsverhalten und mechanismen. PhD thesis, Free University of Berlin, 1996.

Copyright © 2003 Marcel Dekker, Inc.

25. E Zimmermann. Feste Lipid-Nanopartikel—Arzneistoffinkorporation, Charakterisierung und physikalische Stabilität. PhD thesis, Free University of Berlin, 2001.
26. RH Müller, A Dingler. Feste Lipid-Nanopartikel (Lipopearls) als neuartiger Carrier für kosmetische und dermatologische Wirkstoffe. Pharmazeut Zeit Dermopharm 49: 11–15, 1998.
27. A Dingler, GE Hildebrand, J Kielholz, S Gohla, RH Müller. Fluorescence and electron microscopic characterisation of solid lipid nanoparticles in aqueous dispersions and ointments. 2nd World Congress on Emulsion, Bordeaux, 1997, 42:297.
28. A Lippacher, RH Müller, K Mäder. Investigation on the viscoelastic properties of lipid based colloidal drug carriers. Int J Pharm 196:227–230, 2000.
29. A Lippacher, RH Müller, K Mäder. Investigations on semisolid SLN dispersions made from solid-liquid mixtures by means of ESR and rheometry. Proc Int Symp Control Rel Bioact Mater 27:325–326, 2000.
30. A Lippacher. Entwicklung und Charakterisierung von flüssigen und halbfesten SLN-Dispersionen zur topischen Applikation. PhD thesis, Free University of Berlin. 2000.
31. T de Vringer, HAG de Ronde. Preparation and structure of a water-in-oil cream containing lipid nanoparticles. J Pharm Sci 84:466–472, 1995.
32. E Mariani, C. Neuhoff, A Bargagna, F Bonina, M Giacchi, G De Guidi, A Velardita. Synthesis, in vitro percutaneous absorption and phototoxicity of new benzylidene derivatives of 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-one as potential UV sunscreens. Int J Pharm 161:65–73, 1998.
33. L Brinon, S Geiger, V Alard, J Doucet, J-F Tranchant, G Couarraze. Percutaneous absorption of sunscreens from liquid crystalline phases. J Control Rel 6:67–76, 1999.
34. C Bennat, CC Müller-Goymann. Characterization of skin penetration of microfine titanium dioxide used in sunscreen formulations. Proc 2nd World Meeting APGI/APV, Paris, 1998, pp. 859–860.
35. A Dingler, G Hildebrand, H Niehus, RH Müller. Cosmetic anti-aging formulation based on vitamin E–loaded solid lipid nanoparticles. Proc Int Symp Control Rel Bioact Mater 25:433–434, 1998.
36. A Dingler, RP Blum, H Niehus, S Gohla, RH Müller. Solid lipid nanoparticles (SLN/Lipiopearls)—a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. J Microencap 16:751–767, 1999.

Copyright © 2003 Marcel Dekker, Inc.

48

Macroflux Technology for Transdermal Delivery of Therapeutic Proteins and Vaccines

Michel Cormier and Peter E. Daddona
ALZA Corporation, Mountain View, California, U.S.A.

I. INTRODUCTION

It is well documented that the stratum corneum constitutes an impermeable barrier to the permeation of hydrophilic or high-molecular-weight drugs. Many attempts have been made over the years to disrupt this barrier to deliver these molecules through or into the skin. Although chemical permeation enhancers increase skin permeability for some molecules [1,2], their effects are limited at nonirritating concentrations [3]. Many physical methods of permeation enhancement have also been evaluated, including sandpaper abrasion [4] or tape stripping [5] of the skin. While these techniques increase permeability, the degree of their effect on drug absorption is difficult to predict. Other physical methods, such as laser ablation [6], may allow more reproducible results but are cumbersome and expensive. Transdermal delivery systems that incorporate ultrasound [7] and iontophoresis [8] are in development by a number of drug delivery companies for delivery or sampling of small molecules for which pulsatile or on-demand delivery is desired [9]. Although there are reports indicating that delivery of macromolecules is possible with these systems [10], at this stage it is not yet known if these systems will allow successful and reproducible delivery of macromolecules in humans.

Macroflux® technology is a novel transdermal drug delivery method that ALZA Corporation is developing for use with several transdermal delivery systems that may increase the number of drugs that can be delivered across the skin

Copyright © 2003 Marcel Dekker, Inc.

at therapeutically useful rates. The systems incorporate a titanium microprojection array that creates superficial pathways through the skin barrier layer to allow transportation of therapeutic proteins and vaccines, or access to the interstitial fluids for sampling. The microprojection array can be coated with drug or vaccine for bolus or short-duration administration, or it may be used in combination with a drug reservoir for continuous passive or electrotransport applications. Macroflux® systems have been designed for easy, convenient application that yields reproducible delivery of pharmacological agents. Ultimately, Macroflux® systems may enable the delivery of commercially relevant therapeutic proteins and vaccines that currently require parenteral administration.

II. MANUFACTURING

Macroflux® systems are being developed using controlled manufacturing processes incorporating autocad-generated microprojection array design, photo/chemical etching, and forming. First, a thin laminate resist is applied on a sheet of titanium about 30 μm thick. The resist is contact-exposed using a mask with the desired pattern and is then developed—a process very similar to that used in the manufacture of printed circuit boards. The developed sheet is then etched using acidic solutions. After etching, the microprojections are formed to an angle of 90° (relative to the sheet plane) using a forming tool. The finished microprojection array (Fig. 1) is a screen with precision microprojections and adjacent openings that allows drug transport from the reservoir and provides good interface between the skin and the drug reservoir following application. The shape and length of the microprojections and the density and size of the array are easily

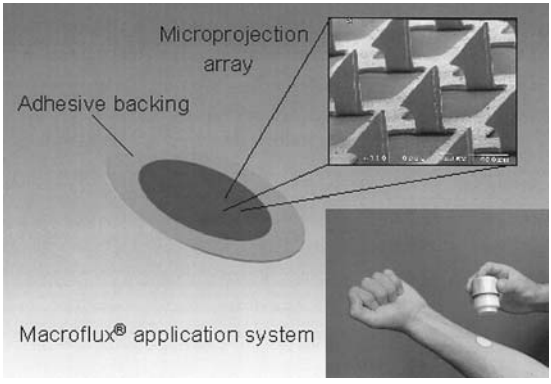


Figure 1 A prototype Macroflux® transdermal system. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

controlled by the design of the mask. Indeed, various characteristics, such as the features illustrated in Figure 1, are easily incorporated into the design. Macroflux® arrays can be up to 5 or 10 cm^2 in area, with up to 320 microprojections/cm^2 and projection lengths of 175–430 μm. The design and length of the microprojections, as well as their density, are chosen specifically for each particular application to optimize delivery and tolerability.

Three types of Macroflux® integrated systems have been designed and tested in preclinical studies. These include: (a) Dry-Coated Macroflux® systems for bolus or short-duration administration that consist of a drug- or vaccine-coated microprojection array adhered to a flexible polymeric adhesive backing, (b) D-TRANS® Macroflux® systems for extended passive delivery that consist of a microprojection array coupled with a drug reservoir, and (c) E-TRANS® Macroflux® systems for pulsatile or on-demand delivery that include a microprojection array coupled with an electrotransport system.

Application of the systems is accomplished manually or, preferably, with a custom-made applicator. Typically, this reusable applicator is spring-loaded and delivers the system with a quick impact to ensure uniformity of penetration through the stratum corneum (Fig. 1).

III. DEVELOPMENT STATUS

Macroflux® systems have been extensively tested in preclinical studies in hairless guinea pigs (HGPs), and early clinical development is ongoing.

The HGP was chosen as the best animal model for Macroflux® preclinical delivery studies because its skin anatomy is more similar to human skin than that of other rodents [11]. In addition, this species has been documented as a good experimental model for drug transport [12,13], contact sensitization [14,15], skin irritation [16], skin infection [17,18], and wound healing [19].

A. Dry-Coated Macroflux®

Dry-Coated Macroflux® systems were evaluated using the model 1200 Da peptide desmopressin. Macroflux® microprojection arrays were coated with an aqueous 30 wt% desmopressin solution and dried. The coated microprojection array was adhered to a flexible polymeric adhesive backing. The system, illustrated in Figure 1, had a total surface area of 8 cm^2 and a 2 cm^2 active (microprojection array) treatment area. Studies in the HGP demonstrated that a therapeutically relevant dose of desmopressin was delivered from Dry-Coated Macroflux® systems after only a 5-s application time. After a 1-h application time, about 18 μg desmopressin was delivered from the same system (Fig. 2).

Copyright © 2003 Marcel Dekker, Inc.

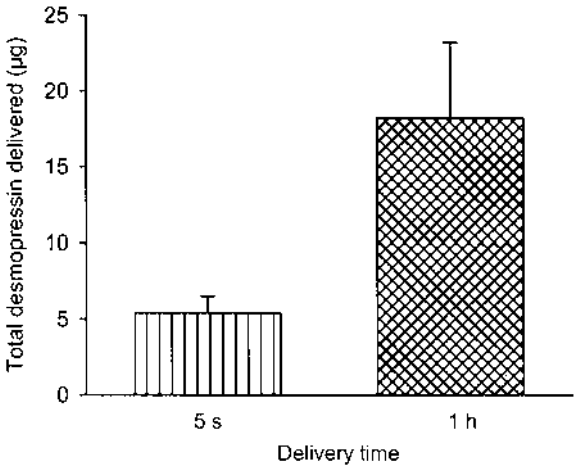


Figure 2 Desmopressin delivery from Dry-Coated Macroflux® systems in the HGP. Desmopressin acetate was delivered from a Dry-Coated Macroflux® system (330 µm microprojection length, 190 microprojections/cm^2, and 2 cm^2 area) for 5 s or 1 h. The total amount of ^{3}H-desmopressin delivered systemically ($n = 3$, mean ± SEM) was determined by measuring urinary excretion of radioactivity for 2 days following system removal and then corrected using the percentage excreted following intravenous injection.

Dry-Coated Macroflux® systems were also evaluated in the HGP using the model protein vaccine ovalbumin (OVA). The microprojection array was coated with an aqueous OVA solution and dried. Control of intracutaneous OVA delivery was achieved through variation in the concentration of the coating solution, wearing time, and system size. Studies in the HGP demonstrated that a range of 1–80 µg of protein was delivered intracutaneously; a delivery rate as high as 20 µg in 5 s was achieved with a 2 cm^2 array (Table 1). Using these delivery conditions, immunization studies were conducted in the HGP with OVA Dry-Coated

Table 1 OVA Delivery in HGP Skin from OVA-Coated Macroflux® Systems[a]

OVA concentration (%)	1	5	20	20
Wearing time	5 s	5 s	5 s	1 h
Surface area (cm^2)	1	1	2	2
Dose delivered (µg)	1	5	20	80

[a] The total amount of OVA delivered in the skin was determined using FITC-labeled OVA.

Copyright © 2003 Marcel Dekker, Inc.

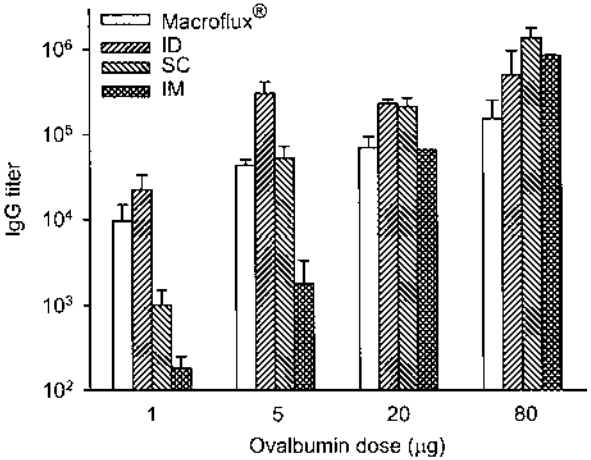


Figure 3 Anti-OVA IgG response to OVA immunization in the HGP. Each animal received a primary immunization followed by a secondary (booster) immunization 4 weeks later with the same test article. The routes of administration were intracutaneous with Dry-Coated Macroflux® (330 μm microprojection length, 190 microprojections/cm^2, and 2 cm^2 area), ID, SC, and IM injection. The serum samples were collected 1 week after the booster and evaluated for the presence of anti-OVA IgG antibodies by ELISA. The results are expressed as end-point antibody titers ($n = 4$, mean ± SEM) relative to nonimmunized control sera.

Macroflux® and compared with identical doses of OVA injected with 25-gauge needles through the intramuscular (IM), subcutaneous (SC), and intradermal (ID) routes. All animals were primed with an initial dose of 1, 5, 20, or 80 μg OVA followed by an identical booster dose 4 weeks later. At 1 week following the booster, all animals showed a seroconversion with specific anti-OVA antibody titers. At 1- and 5-μg doses, the antibody response observed with Macroflux® administration was equivalent to ID dosing, and up to 100-fold higher than that observed following SC or IM administration (Fig. 3).

B. D-TRANS® Macroflux®

D-TRANS® Macroflux® systemic delivery of the peptide desmopressin and of an antisense oligonucleotide (6800 Da) were evaluated in the HGP. A hydrogel matrix reservoir containing various concentrations of desmopressin acetate or oligonucleotide was intercalated between the microprojection array and the backing layer, and the systems were applied to HGP skin for 4 h and 24 h, respectively.

Copyright © 2003 Marcel Dekker, Inc.

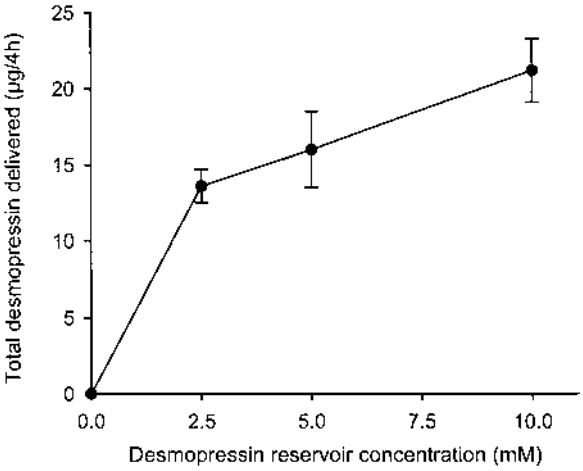


Figure 4 Desmopressin delivery from D-TRANS® Macroflux® systems in the HGP. Desmopressin acetate was formulated in 2% HEC and delivered from a D-TRANS® Macroflux® system (330 µm microprojection length, 190 microprojections/cm^2, and 2 cm^2 area) for 4 h. The total amount of ^{3}H-desmopressin delivered systemically (n = 3, mean ± SEM) was determined as in Figure 2.

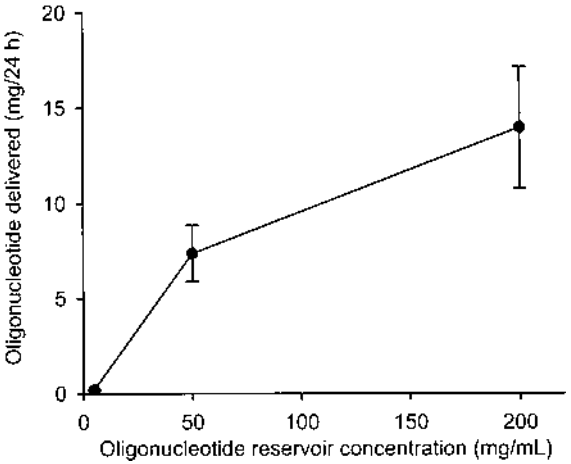


Figure 5 Antisense oligonucleotide delivery from D-TRANS® Macroflux® systems in the HGP. The antisense oligonucleotide tested, a 20-mer with a phosphorothioate backbone, was formulated in 2% HEC and delivered from a D-TRANS® Macroflux® system (430 µm microprojection length, 241 microprojections/cm^2, and 2 cm^2 area) for 24 h. The total amount of ^{3}H-oligonucleotide delivered systemically (n = 3, mean ± SEM) was determined by measuring the radioactive content in the liver and then corrected from the percentage present in the liver following intravenous injection.

Copyright © 2003 Marcel Dekker, Inc.

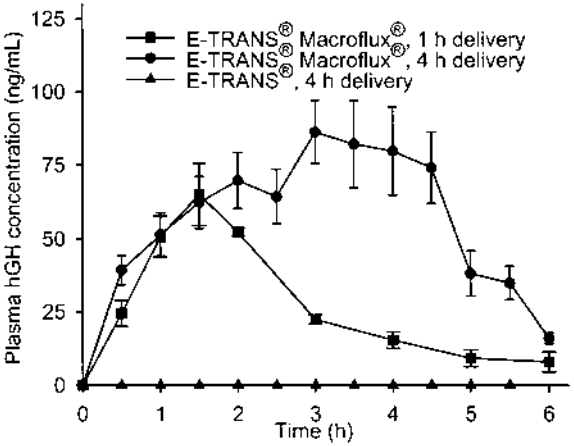


Figure 6 hGH delivery from E-TRANS® Macroflux® systems in the HGP. E-TRANS® Macroflux® or E-TRANS® systems were applied for either 1 or 4 h. A microprojection array (430 μm microprojection length, 241 microprojections/cm^2, and 2 cm^2 area) was adhered to the skin side of the hGH-containing hydrogel. The animals were anesthetized for the entire duration of the experiment, and blood samples were taken at various times and subsequently analyzed by RIA for hGH content. Data are expressed as mean ± SEM (n = 3–6).

Systemic delivery of desmopressin from D-TRANS® Macroflux® systems was found to be concentration dependent. After 4 h, up to 20 μg desmopressin was delivered from a 10 mM desmopressin hydrogel (Fig. 4). Control experiments demonstrated undetectable transport from the same formulations in the absence of the microprojection array. Additional experiments (data not shown) demonstrated that elimination and metabolism of the peptide were similar following intravenous (IV) or D-TRANS® Macroflux® administration. Pharmacokinetic experiments showed very rapid onset with peak serum levels 1 h after system application. In addition, identical pharmacological activity (reduction of urine volume and increase of urine osmolality) was demonstrated following IV and Macroflux® administration of desmopressin.

Systemic delivery of the oligonucleotide from D-TRANS® Macroflux® systems was also found to be concentration dependent. After 24 h, about 14 mg oligonucleotide was delivered from a 2 cm^2 system containing a 200 mg/mL oligonucleotide hydrogel (Fig. 5). Control experiments demonstrated undetectable transport from the same formulation without Macroflux® technology.

Copyright © 2003 Marcel Dekker, Inc.

C. E-TRANS® Macroflux®

A custom-built silver/silver chloride 100 μA/cm^2 iontophoresis system was used in combination with Macroflux® to deliver the therapeutic protein human growth hormone (hGH) to HGPs. hGH was formulated at 1 mM in a hydrogel and delivered from the cathodic electrode.

When the systems were applied to HGP skin and activated, Macroflux® technology enabled electrotransport of hGH. Both the 1- and 4-h delivery patterns yielded rapid appearance of hGH in plasma with little skin depot observed upon system removal. From these data, pharmacokinetic calculations demonstrated systemic absorption of 24 ± 2 and 39 ± 6 μg of hGH, respectively. When the same electrotransport conditions were used to deliver hGH without Macroflux® technology, no significant hGH blood levels were detected (Fig. 6).

IV. DISCUSSION AND CONCLUSION

Results obtained with Macroflux® in preclinical studies demonstrate that the system is capable of enhancing the transdermal delivery of peptides, proteins, and oligonucleotides. While OVA is a 45-kDa protein that does not permeate normal skin to any significant extent, Dry-Coated Macroflux® allowed controlled intradermal delivery of OVA in HGPs. Significant delivery was observed within a few seconds of system application, and antibody levels were similar to those produced by intradermal injection. Intradermal injection is technically demanding and not widely used in the clinical setting; Dry-Coated Macroflux® may be an attractive alternative to intradermal delivery of boluses such as vaccines or potent pharmacological agents. In addition, Dry-Coated Macroflux® may allow smaller immunizing doses as compared to SC or IM injections. It is noteworthy that this dose-sparing effect observed with ID administration of OVA has been observed by investigators using other antigens [20].

Results obtained with desmopressin and hGH also demonstrate that systemic transdermal delivery of peptides and proteins is possible in the HGP model. With desmopressin, doses relevant to human therapy were delivered in only a few hours. hGH, a 22-kDa protein, is believed to be a good model for very potent cytokines such as interferons.

Macroflux® technology has also been tested using different classes of compounds such as oligonucleotides and polysaccharides. With oligonucleotides, delivery of 14 mg was achieved in 24 h using a 2 cm^2 microprojection array. This dose is therapeutically relevant, and Macroflux® technology may represent a significant opportunity for delivery of this challenging class of compounds.

In addition to drug and vaccine delivery, Macroflux® technology may also have applications for sampling analytes in biological fluids. Indeed, the Macro-

Copyright © 2003 Marcel Dekker, Inc.

flux® system is minimally invasive and is particularly suited for access to the interstitial fluids.

In all the preclinical animal studies presented here, the Macroflux® system was well tolerated. In addition, no signs of infection were observed in any of the animals. Two short-term wearing studies of placebo systems have also been conducted in humans with comparable results.

In conclusion, Macroflux® technology may help overcome transdermal delivery challenges by increasing the number of drugs that can be delivered across the skin at therapeutically useful rates. The technology allows bolus or short-duration administration from a drug- or vaccine-coated system, or it may be used in combination with a drug reservoir for continuous passive or electrotransport applications. Ultimately, Macroflux® systems may enable successful delivery of commercially relevant therapeutic proteins and vaccines that currently require parenteral administration.

ACKNOWLEDGMENT

The authors gratefully acknowledge the contributions of their co-workers for expert technical assistance, particularly WeiQi Lin, Jim Matriano, Bonny Johnson, Creag Trautman, Ahmad Samiee, Wendy Young, Margaret Buttery, Kofi Nyam, and Angie Griffin, as well as Jennifer Wright for manuscript preparation.

REFERENCES

1. AC Williams, BW Barry. Skin absorption enhancers. Crit Rev Ther Drug Carr Syst 9:305–353, 1992.
2. LR Hsu, YH Tsai, YB Huang. The effect of pretreatment by penetration enhancers on the in vivo percutaneous absorption of piroxicam from its gel form in rabbits. Int J Pharm 71:193–200, 1991.
3. P Xu, YW Chien. Enhanced skin permeability for transdermal drug delivery: physiopathological and physicochemical considerations. Crit Rev Ther Drug Carr Syst 8: 211–236, 1991.
4. FL Tse, R Laplanche. Absorption, metabolism, and disposition of [14C]SDZ ENA 713, and acetylcholinesterase inhibitor, in mini pigs following oral, intravenous, and dermal administration. Pharm Res 15:1614–1620, 1998.
5. F Kompaore, C Dupont, JP Marty. In vivo evaluation in man by two noninvasive methods of stratum corneum barrier function after physical and chemical modifications. Int J Cosm Sci 13:293–302, 1991.
6. JS Nelson, JL McCullough, TC Glenn, WH Wright, LH Liaw, SL Jacques. Mid-infrared laser ablation of stratum corneum enhances in vitro percutaneous transport of drugs. Invest Dermatol 97:874–879, 1991.

Copyright © 2003 Marcel Dekker, Inc.

7. S Mitragotri, J Farrell, H Tang, T Terahara, J Kost, R Langer. Determination of threshold energy dose or ultrasound-induced transdermal drug transport. J Control Rel 63:41–52, 2000.
8. SK Gupta, G Sathyan, B Phipps, M Klausner, M Southam. Reproducible fentanyl doses delivered intermittently at different time intervals from an electrotransport system. J Pharm Sci 88:835–841, 1999.
9. RH Haak, SK Gupta. Pulsatile drug delivery from electrotransport therapeutic systems. In: R Gurny, HE Junginger, NA Pappas, eds. Pulsatile Drug Delivery: Current Applications and Future Trends. Stuttgart: Wissenschaftliche Verlagsgesellschaft mbH, 1993, pp. 99–112.
10. S Mitragotri, D Blankschtein, R Langer. Ultrasound-mediated transdermal protein delivery. Science 269:850–853, 1995.
11. H Suekt, C Gammal, K Kudoh, AM Kligman. Hairless guinea pig skin: anatomical basis for studies of cutaneous biology. Eur J Dermatol 10:357–364, 2000.
12. S Kumar, H Char, S Patel, D Piemontese, K Iqbal, AW Malick, E Neugroschel, CR Behl. Effect of iontophoresis on in vitro skin permeation of an analogue of growth hormone releasing factor in the hairless guinea pig model. J Pharm Sci 81:635–639, 1992.
13. KC Moon, RC Webster, HI Maibach. Diseased skin models in the hairless guinea pig skin: in vivo percutaneous absorption. Dermatologica 180:8–12, 1990.
14. H Miyauchi, T Horio. A new animal model for contact dermatitis: the hairless guinea pig. J Dermatol 19:140–145, 1992.
15. DF Woodward, AL Nieves, LS Williams, CS Spada, SB Hawley, JL Duenes. A new hairless strain of guinea pig: characterisation of the cutaneous morphology and pharmacology. In: HI Maibach, NJ Lowe, eds. Models in Dermatology. Vol. 4. Basel: Karger, 1989, pp. 71–78.
16. A Fullerton, J Serup. Topical D-vitamins: multiparametric comparison of the irritant potential of calcipotriol, calcitriol in a hairless guinea pig model. Contact Dermat 36:184–190, 1997.
17. PJ Bobrowski, R Capiola, YM Centifanto. Latent herpes simplex virus reactivation in the guinea pig: an animal model for recurrent disease. Int J Dermatol 30:29–35, 1991.
18. H Hanel, B Braun, K Loschkorn. Experimental dermatophytosis in nude guinea pigs compared with infections in pigbright white animals. Mycoses 33:179–189, 1990.
19. SK Brantley, SF Davidson, SK Das. A dose-related curve of wound tensile strength following ultraviolet irradiation in the hairless guinea pig. Am J Med Sci 302:75–81, 1991.
20. EA Henderson, TJ Louie, K Ramotar, D Ledgerwood, KM Hope, A Kennedy. Comparison of higher-dose intradermal Hepatitis B vaccination to standard intramuscular vaccination of healthcare workers. Infect Control Hosp Epidemiol 21:264–269, 2000.

Copyright © 2003 Marcel Dekker, Inc.

49
Needle-Free Drug Delivery

Franklin Pass
Antares Pharma, Inc., Minneapolis, Minnesota, U.S.A.

John Hayes
aForte, Chanhassen, Minnesota, U.S.A.

I. INTRODUCTION

The ability to deliver medicines by needle-free jet injection has been understood for decades, yet this technology has never been widely adopted by health care providers. Obstacles to successful commercialization have included the high price of injectors, the large size and complexity of the injectors, and the fears of physicians and pharmaceutical decision makers regarding their reliability. Furthermore, until 1986, the only drug routinely self-injected in the home, where needle-free delivery has the greatest appeal, was insulin. The dynamics of the insulin marketplace, driven by the low cost of insulin, favored less expensive injection systems. The technology was kept afloat by a few very small, poorly capitalized companies focused upon modest sales within the small population of strongly needle-adverse people with diabetes. However, the true opportunity of needle-free jet injection extends well beyond this niche group.

Additional negative influences discouraged investment in the technology. The common practice of jet-injected mass immunization in the military was far from painless and remains an unpleasant memory for many. In addition, the spread of infectious diseases by contaminated nozzles has been reported after mass immunization [1], so the use of the devices in a hospital, clinic, or military immunization program has seemed impractical. Therefore, the scope of this chapter will be limited to observations regarding the utility of this technology for self-injection in the home and will ignore the small numbers of largely unpublished attempts to design a safe jet injector for mass immunization, a continuing goal of public health institutions.

Copyright © 2003 Marcel Dekker, Inc.

The marketplace has changed in recent years, and the market opportunities for needle-free jet injection look considerably more attractive today. Change has been driven by the recent introduction of bioengineered medications, usually proteins that cannot be administered orally and must be taken on a chronic basis. Growth hormone for the treatment of growth retardation, for example, is administered by daily injection to children, a remarkably needle-adverse population. Bioengineered drugs, including new analogs of insulin, are more expensive than traditional medications and provide suitable sales margins to justify an investment by pharmaceutical manufacturers in more costly delivery systems.

These market changes have stimulated new investment in improving the technology, and several new jet injectors for insulin and growth hormone have been introduced to the market in recent years. Sales are increasing, but market share remains relatively small. Several large pharmaceutical companies are lending financial support to device-engineering programs and actively testing new products and prototypes.

Antares Pharma, Inc. has been one of the pioneers in developing needle-free jet injectors. The company has manufactured and distributed insulin injectors since 1979 and growth hormone injectors since 1994. During the past 8 years, Antares invested approximately $15 million in new engineering research aimed to make the personal jet injector smaller, less expensive, more reliable, and easier to use. This chapter will present certain aspects of our technology progress.

II. HISTORICAL DEVELOPMENT

The discovery of needle-free jet delivery has been attributed to Arnold Sutermeister, who was painlessly struck in the hand with a high-pressure jet water stream in the early 1930s [2]. However, the technology was first popularized by Robert A. Hingson, a Cleveland physician, and Frank H.J. Figge, a Baltimore professor of anatomy, almost 20 years later [3,4]. Patents in the field were purchased by E.R. Squibb & Sons, Becton Dickinson Company, and R.P. Scherer Company. Scherer developed and sold a coil spring needle-free device called the Hypospray from 1961 until 1971. Neither Squibb nor Becton Dickinson Company commercialized their technology.

Hingson and Hughes in 1947, Perkin et al. in 1950, and Weller and Linder in 1960 published studies of needle-free insulin delivery [3,5,6], while additional investigators published data on the needle-free injection of local anesthetics and other medications [7,8]. Over the years, investigators have documented the pharmacokinetics and clinical responses with various insulins, including analog insulin administration [9,10]. Recently, the efficacy and high level of patient acceptance of needle-free growth hormone delivery have been reported [11,12].

Copyright © 2003 Marcel Dekker, Inc.

Antares traces its origins to 1972, although its first sales of a rather large, heavy stainless-steel device began in 1979. The company currently manufactures and sells the seventh-generation device, a composite plastic injector with a replaceable plastic needle-free syringe. A prototype of the eighth-generation injector is just entering clinical evaluation. Each new generation of injectors has resulted in a simpler, more compact device, and the retail price of an injector has fallen from $1200 in 1979 to $300 today. Since manufacturing costs are influenced greatly by volume, wide acceptance of jet injection would likely result in further price reductions.

III. DESCRIPTION OF TECHNOLOGY

The Antares injector is a coil spring device approximately the size and shape of a small flashlight. Figure 1 illustrates the seventh-generation injector beside the smaller eighth-generation prototype. The injector accepts a polycarbonate plastic syringe with a very snug piston plunger. The syringe incorporates a precisely molded small orifice where a conventional syringe would host a needle. The coil spring supplies the energy to operate the device, rapidly forcing liquid through the syringe orifice on release. This forms a "liquid needle" at pressures sufficient to penetrate the skin surface.

Figure 1 A comparison of the Antares needle-free jet injector and the next-generation injector prototype.

Copyright © 2003 Marcel Dekker, Inc.

To operate, one compresses the spring, fills the injector with a single dose of medication through a plastic adapter inserted in a standard medication vial, and then, holding the injector perpendicular to the skin surface, presses the trigger button. In a fraction of a second, volumes to 0.5 mL are delivered with very little to no pain. Similar to a needle, bruising or bleeding may be observed at the injection site, but proper training and practice greatly reduces complications, as well as the chances of an incomplete injection.

IV. RESEARCH AND DEVELOPMENT

The design of jet injectors remains an empirical exercise, a balance between spring force and nozzle orifice diameter, to minimize the energy of injection without compromising the pressure needed to penetrate the skin surface. Too large a spring force creates unpleasant noise and vibration, while too large an orifice causes pain and bleeding. The thickness and penetrability of human skin varies from body site to body site and also from one individual to another, so clinical trials of prototype devices are required to insure that everyone will receive complete injections. Performance data gathered from clinical trials of earlier commercial injectors were recently published [13].

The 1990s were marked by a breakthrough in the cost and functionality of jet injectors based upon advances in materials. Jet injectors are high-energy machines; the injector body vibrates during each injection and requires twisting to rearm the coil spring. Steel injectors withstood the shock and wear of twisting without deformity, but had many disadvantages. They were heavy, the drug chamber required periodic boiling to sterilize it, and the patient could not see the drug in the chamber. In the mid-1990s, the steel injector was replaced by a composite plastic injector. Injector size, weight, and winding torque, i.e., the work needed to compress and arm the spring, were reduced by half.

The greatest engineering challenge was to find suitable materials to replace the steel drug chamber. A robust design for a transparent, needle-free syringe must withstand the rapid force of injection without shattering or stretching, and the common syringe materials, glass and polypropylene, failed these tests. Polycarbonate syringes, introduced in 1997, have proven adequate, although attention to small details in mold design is needed to maintain a uniform liquid stream and avoid fracturing.

Antares manufactures approximately 5000 injectors and less than one million syringes annually. Today, the assembly and packaging processes are manual. Larger volumes will require automated assembly and result in lower manufacturing costs.

Copyright © 2003 Marcel Dekker, Inc.

V. CLINICAL EXPERIENCE

Attempts to improve injector design through experiments in laboratory models of excised human skin, rubberized materials, or even pork bellies have been of limited value. Most commonly the company constructs a functional one-off model of a new design and tests its performance with saline in groups of volunteer subjects. The design is further improved following each of two or three such clinical trials before a prototype is built.

Over the years, many investigators have compared the pharmacokinetics of jet delivery to conventional needle drug delivery. Pehling and Gerich [9] were able to show somewhat earlier uptake of insulin, while Houdijk et al. [11] could show no differences in growth hormone kinetics.

VI. REGULATORY ISSUES

New injector designs are considered substantially equivalent to earlier marketed devices and thus maintain a FDA 510K status. In the late 1990s, Antares received ISO9001 and ENS46,001 certification of its manufacturing processes. Antares believes that more stringent regulations may be imposed by regulatory bodies if the injector is paired with a drug not yet approved for use.

VII. TECHNOLOGY POSITION

Pharmaceutical and device manufacturers have invested heavily in alternatives to conventional needle delivery. The delivery of insulin by infusion pump has helped many people with insulin control problems. Inhaled insulin, now in phase III clinical evaluation, is another example of an alternative delivery approach. Nevertheless, Antares believes that needle-free delivery is well accepted by patients and newer devices will be equally competitive to nasal or pulmonary delivery. The competitive advantage will be lower cost and less potential risk.

Two British device companies have been developing novel needle-free systems during the 1990s, one based upon the injection of dry powder through the skin and the other using liquid packaged as a single-dose glass vial in a disposable injector. The delivery of dry powder is convenient if the drug is lyophilized and then requires reconstitution before delivery. Use of a glass cartridge is well accepted as a long-term storage container, unlike the polycarbonate used in the Antares needle-free syringes. However, neither technology has yet to reach the market.

Copyright © 2003 Marcel Dekker, Inc.

VIII. FUTURE DIRECTIONS

Antares is developing two new injector systems. One system, planned to be the eighth-generation insulin injector system, further reduces the size and complexity of the injector and incorporates an insulin cartridge system. This injector closely resembles the insulin "pens" now common in the European market and increasingly found in the United States.

The second system is based upon the combination of a very small, hidden needle with pressure injection. Much of the variability of injection within a single individual and from person to person can be traced to the dead cell layer, the stratum corneum, at the skin surface. Once this tough, dry barrier is pierced by a small needle, the dispersion of drug in a jet-like pattern can be achieved with much lower energy expenditures. As a result, it may be feasible to accomplish jet injection directly from modified glass cartridges. Antares has manufactured a prototype disposable, single-dose "minineedle" injector and begun clinical evaluation.

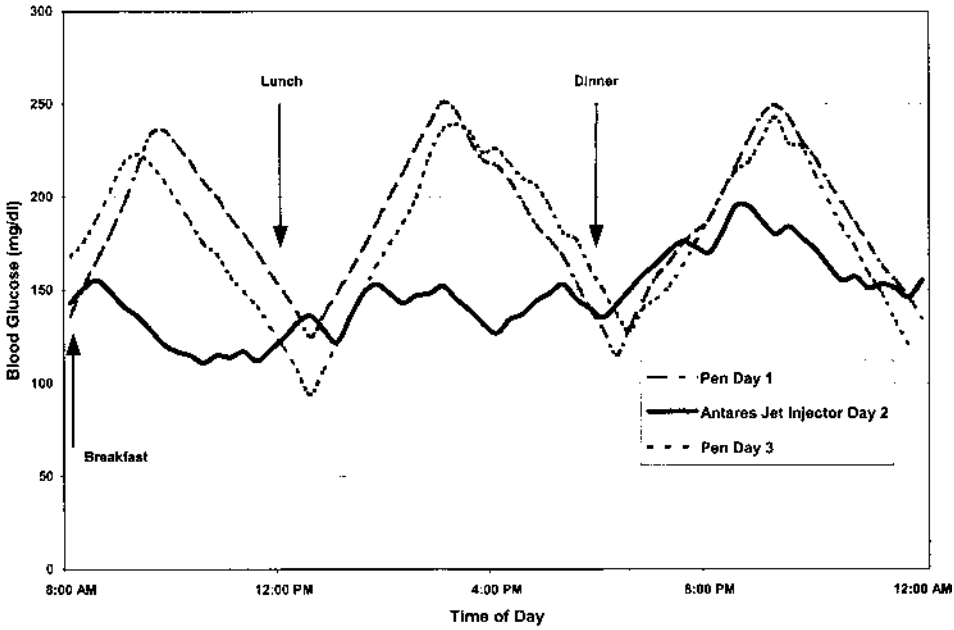


Figure 2 Blood glucose levels recorded in a single subject treated with the same dose of regular insulin over a 3-day period. The subject used a conventional needle and syringe on Days 1 and 3 and an Antares needle-free jet injector on Day 2.

Copyright © 2003 Marcel Dekker, Inc.

Can the needle-free jet injection of insulin offer therapeutic advantage over conventional needle delivery? In the past, Antares has not had the resources to organize and support long-term outcome studies in people with diabetes. However, the introduction of a continuous glucose monitor by MiniMed has allowed investigators to quickly compare needle and needle-free insulin delivery. Figure 2 shows a comparison of blood sugar levels in a single subject with type 1 diabetes, using regular insulin before meals and a needle on Days 1 and 3 and a MediJector on Day 2. This subject, who was part of a larger clinical study, experienced an average 30 mg/dL reduction of his blood sugar the day he used the MediJector. This reduction might translate to a 1% reduction in glycosylated hemoglobin and a 12% reduction in complications, according to outcome studies in type 2 diabetics [14]. Complications such as renal failure, blindness, and cardiovascular disease might be averted or delayed if the blood glucose reduction could be sustained indefinitely by needle-free delivery. Similar results might be achieved with conventional needles by substituting rapid-acting analog insulin for regular insulin, but this would require more daily injections at a greater expense. These data were collected by Dr. Mario Velussi, an Italian diabetologist (unpublished information). Further studies are underway to corroborate these promising results.

In summary, needle-free drug delivery technology is undergoing significant improvements with the promise of mainstream adoption as a safe, reliable, and economical alternative to conventional needle delivery. This evolution has occurred at a point in time when a myriad of new bioengineered drugs demand better delivery systems.

REFERENCES

1. J Canter, K Mackey, LS Good, RR Roberto, J Chin, WW Bond, MJ Alter, JM Horan. An outbreak of hepatitis B associated with jet injections in a weight reduction clinic. Arch Intern Med 150:1923–1927, 1990.
2. RH Hingson, FHJ Figge. A survey of the development of jet injection in parenteral therapy. Curr Res Anesth Analg 31:361–366, 1952.
3. RA Hingson, JG Hughes. Clinical studies with jet injection: a new method of administration. Curr Res Anesth Analg 26:221–230, 1947.
4. FHJ Figge, DJ Barnett. Anatomic evaluation of a jet injection instrument designed to minimize pain and inconvenience of parenteral therapy. Am Pract 3:197–206, 1948.
5. GS Perkin, GM Todd, TM Brown. Jet injection of insulin in the treatment of diabetes mellitus. Proc Am Diab Assoc 10:184–199, 1950.
6. C Weller, M Linder. Jet injection of insulin versus the syringe-and-needle method. JAMA 195:156–159, 1966.
7. PM Margetis, EP Quarantillo, RB Lindberg. Jet injection local anesthesia in dentistry. US Armed Forces Med J 9:625–634, 1958.
8. H von Pietschmann. Erfahrungen mit dem “Hypospray Jet Injector” in der lokalen

Copyright © 2003 Marcel Dekker, Inc.

prednisolon-therapie rheumatischer erkrankungen. Wien Z Int Med 45:348–352, 1964.
9. GB Pehling, JE Gerich. Comparison of plasma insulin profiles after subcutaneous administration of insulin by jet spray and conventional needle injection in patients with insulin-dependent diabetes mellitus. Mayo Clin Proc 59:751–754, 1984.
10. EI Felner, JL Gonzalez. Comparison of jet stream Medi-Jector and conventional insulin syringe using Humalog insulin. Diab Res 34:113–123, 1999.
11. ECAM Houdijk, E Herdes, HA Delemarre-Van de Waal. Pharmacokinetics and pharmacodynamics of recombinant human growth hormone by subcutaneous jet- or needle-injection in patients with growth hormone deficiency. Acta Paediatr 86: 1301–1307, 1997.
12. GH Verrips, RA Hirasing, M Fekkes, T Vogels, SP Verloove-Vanhorick, HA Delemarre-Van de Waal. Psychological response to the needle-free Medi-Jector or the multidose Disetronic injection pen in human growth hormone therapy. Acta Paediatr 87:154–158, 1998.
13. DL Bremseth, F Pass. Delivery of insulin by jet injection; recent observations. Diab Tech Ther 3:225–232, 2001.
14. UKPDS 33. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 352:837–853, 1998.

Copyright © 2003 Marcel Dekker, Inc.

50
Dermal PowderJect Device

Brian John Bellhouse and Mark A. F. Kendall
PowderJect Centre for Gene and Drug Delivery Research, University of Oxford, Oxford, England

I. INTRODUCTION

Despite advances in drug formulation, most drugs are delivered in liquid form subcutaneously, by needle and syringe. Many patients dislike this method of administration, but liquid jet injectors are no less painful. Drug delivery using patches and diffusion through the skin has the merit of being painless, but is suitable only for drugs of low molecular weight, and this excludes the majority of drugs and vaccines.

The PowderJect system of transdermal delivery of powdered drug involves the propulsion of solid drug particles into the skin by means of a high-speed gas flow. This needle-free method of transdermal drug delivery is painless, causes no bleeding, and causes negligible damage to the skin. This chapter describes the early prototypes and their use for the injection of a range of powdered drugs and vaccines in model skin and preclinical and clinical studies.

Broad patents have been granted for the delivery of drugs and genes to skin or mucosal surfaces by the PowderJect method.

II. HISTORICAL DEVELOPMENT

The transfection of mammalian or plant cells in large numbers is a very slow process if each cell is injected by needle individually, and electroporation is not easily adapted to intact tissue. Sanford and Klein [1] used a modified 0.22-in. rifle to deliver DNA coated onto tungsten or gold particles (1–3 μm in diameter) at sufficient velocity to penetrate the target tissue. The cartridge was modified

Copyright © 2003 Marcel Dekker, Inc.

by removing the metal bullet and replacing it with a plastic macroprojectile. The DNA/gold particles were attached to the outer surface of the macroprojectile. When the gun was fired, the macroprojectile was accelerated in the barrel of the gun until it hit a stopper plate at the muzzle of the gun, causing the macroprojectile to decelerate rapidly and catapult the DNA/gold particles into the target tissue. A few hundred of the many thousands of DNA/gold particles would penetrate the target cells with subsequent incorporation of the DNA into the cell nuclei.

The use of compressed gas to accelerate solid drug particles through a convergent-divergent nozzle was reported by Bellhouse et al. [2]. Using compressed helium, drug particle velocities of up to 800 m/s were obtained at the nozzle exit [3] and, provided the particles were sufficiently large (10–100 μm in diameter) to compensate for their low density (about 1 g/cm^3), good penetration of the target skin was obtained.

The main challenge in the development of the dermal PowderJect devices for both drug and gene delivery has been to provide a large enough target area (10 mm diameter or more) so that up to 3 mg of drug can be delivered without overloading the skin, with control of particle penetration and good bioavailability.

III. POWDERJECT TECHNOLOGY

A. Core Technology

The core technology involves the high-velocity injection of particle-formulated drugs or vaccines into any physically accessible tissue. These may be for therapy or prevention of disease and may be small molecules, peptides, proteins, or genes. The basic principle is that solid-form particles can be painlessly and effectively delivered into the body if they are appropriately formulated and are travelling at a sufficiently high velocity. This principle can be applied to deliver any drug or vaccine that can be formulated as a solid particle of the appropriate size, mass, density, and strength. By using the appropriate PowderJect system, this technique may be employed to deliver a range of drugs into the skin (transdermal), the tissues of the mouth and vagina (transmucosal), or directly into other tissues via catheter or minimally invasive surgical entry.

B. Dermal PowderJect Device

A sectional diagram illustrating the design of an early prototype dermal PowderJect device and its key components is shown in Figure 1.

Actuation of the PowderJect system opens a gas canister, which allows helium gas at high pressure to enter a chamber at the end of which is a drug

Copyright © 2003 Marcel Dekker, Inc.

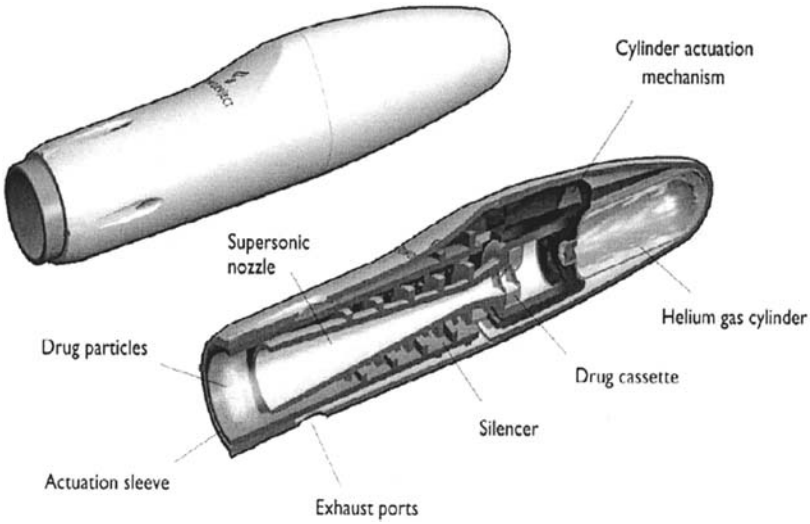


Figure 1 Outline diagram of a prototype PowderJect device with a conical divergent nozzle.

cassette containing the powdered drug or vaccine between two polycarbonate membranes. At the designed release pressure, virtually instantaneous rupture of both membranes causes the gas to expand rapidly, forming a strong shock wave that travels down the nozzle at speeds of up to 600–900 m/s. This shock wave initiates a nozzle-starting process followed by supersonic flow, up to Mach 3, which serves to accelerate the particles to high velocity [4].

The particles have sufficient momentum to penetrate the skin while the helium gas is reflected into a silencer. Individual tiny particles of powder pass through the outer layer of the skin (stratum corneum), penetrating down to the required level in the tissue. The drug dissolves and then either acts locally or diffuses into the bloodstream to deliver its therapeutic effect.

C. Targeted Delivery to Skin Layers

Skin consists of several layers. Beneath the outer keratinous stratum corneum, which consists of dead cells and is the body's main barrier to drug delivery, is an outer epidermis and an inner dermis. The epidermis is a thin epithelial membrane. The dermis is a thicker layer and is comprised of connective tissue. A deep extension of the dermis, the subcutaneous layer, anchors the skin to the underlying tissues.

Copyright © 2003 Marcel Dekker, Inc.

Most drugs with a systemic action, such as proteins and peptides, are ideally delivered to the dermis to target the area with the highest density of blood capillaries. Conventional and DNA vaccines are ideally delivered into the epidermis.

The PowderJect system delivers an intradermal injection. The depth of penetration of the drug particles is optimized by adjusting the momentum density of the particles within the gas flow. Particle mass and area are controlled through formulation and processing of the drug. Particle velocity is controlled within the device by three parameters: nozzle geometry, membrane burst strength, and gas pressure.

Drugs that require self-administration, or local delivery to sensitive sites, can be made more attractive for the patient with this technology.

IV. RESEARCH AND DEVELOPMENT

An integrated review of the medical, pharmacological, and engineering aspects of the technology has been given by Burkoth et al. [5]. The paper includes descriptions of clinical trials in which efficacious delivery was achieved for lidocaine, a local anesthetic, and encouraging results were obtained for alprostadil, which is used in the treatment of male erectile dysfunction. Recently, Kendall et al. [6] have described fundamental investigations of the biomechanics of powder injection, using a calibrated piston-based test system to propel particles into excised skin at known velocities up to 260 m/s. It was demonstrated in these experiments that particles could penetrate the stratum corneum (the tough outermost layer of the skin) to reach underlying tissue, and the dependence of penetration depth on particle velocity, size, and density was characterized.

This interaction between high-velocity drug particles and biological tissue is one essential facet of the complete powder injection system. The means of imparting momentum to the powdered drug dose is equally important. In the practical drug delivery device to be discussed here, particles are accelerated by entrainment in a high-speed gas flow. Particular aspects of the fluid dynamics of certain devices have been discussed by Bellhouse et al. [7], Kendall et al. [8] and Quinlan et al. [3].

A. Prototype Devices Tested

The configuration of a clinical device for transdermal powdered drug delivery is shown in Figure 1. The key components of the device are a gas reservoir, in which compressed helium is stored, typically at a pressure of tens of atmospheres; a drug cassette, in which the powdered drug is retained between a pair of bursting membranes; and a convergent-divergent nozzle. Basic compressible flow theory provides a qualitative description of this system's expected mode of operation.

Copyright © 2003 Marcel Dekker, Inc.

When gas is released from the reservoir, a large pressure difference builds up across the drug cassette. The membranes rupture, leading to the formation of a shock wave, which propagates down the nozzle and initiates an unsteady high-speed gas flow, as in a classical shock tube. Later, a sustained bulk flow of gas from the cylinder is established, and under certain conditions, the device's convergent-divergent nozzle functions as a supersonic nozzle. In the course of these processes, particles are entrained in the gas flow and accelerate toward the nozzle exit. As the particle-laden flow impinges on the skin, gas is deflected away to the side and vents to the atmosphere through a silencer. The particles, with their relatively large inertia, maintain a high axial velocity and penetrate the tough outer layer of dead cells (the stratum corneum), coming to rest in deeper layers of the skin. There, the drug either acts locally, or diffuses into the bloodstream for systemic effect.

B. Experimental and Analytical Methods

The gas and particle dynamics of the PowderJect system were originally investigated experimentally by Bellhouse et al. [7] and Quinlan et al. [3] and in more detail by Kendall et al. [4]. The configuration of the prototype device whose testing we describe in this section is illustrated in Figure 2. In contrast with the production design shown in Figure 1, this prototype features an annular valve at the downstream end of the cylindrical reservoir, connecting the reservoir to the rupture chamber. The prototype was tested without a silencer for the purposes of investigation. The nozzle had a conical divergent section with an exit-to-throat area ratio of 20:3. The dermal PowderJect prototype was instrumented with wall-mounted pressure transducers and a Pitot probe with the aim of quantifying the gas flowfield (Fig. 2). Further insights into the two-dimensional nature of the gas flowfield and, to a lesser extent, the gas flowfield's interaction with particles were obtained with a Schlieren imaging system.

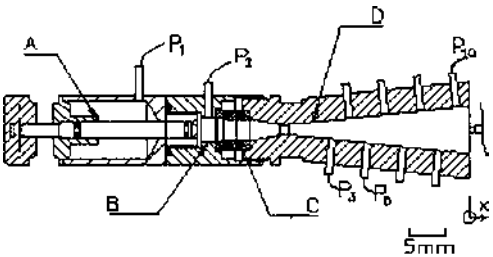


Figure 2 Schematic of an early dermal PowderJect prototype instrumented for pressure measurements [4]. The static pressure transducers are labeled P_1–P_{10}.

Copyright © 2003 Marcel Dekker, Inc.

The particle velocity field, which is ultimately the most important mechanical operating characteristic of the device, was measured using Doppler global velocimetry (DGV) in the jets generated by the conical nozzle. Overviews of the evolution of DGV and the current state of the art have been published [9,10].

C. Measured Gas and Particle Flows

Sample pressure measurements at three nozzle locations are shown in Figure 3. Such measurements throughout the system quantify the gas-flow regimes and structure. One important parameter of the gas flow obtained from the pressure measurements is the axial gas flow Mach number. Axial profiles of Mach number at various times in the flow are compared with flow from an ideal, isentropic expansion in Figure 4. It can be seen that a maximum gas flow Mach number of 3 is achieved.

Sequences of Schlieren images such as the sample shown in Figure 5 reveal the structure of the evolving flowfield with greater detail and clarity. Flow is from left to right.

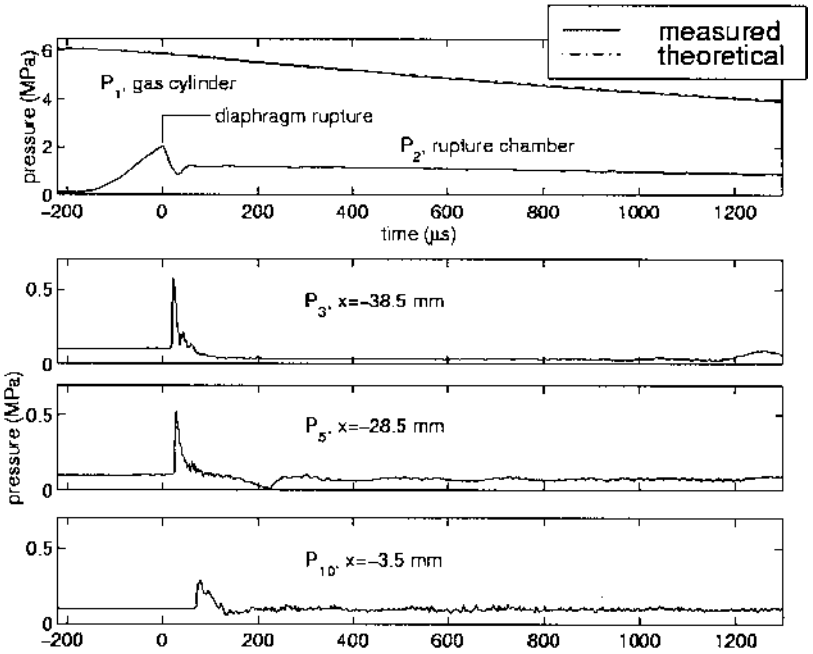


Figure 3 Measured and calculated pressures within the prototype dermal PowderJect system [4].

Copyright © 2003 Marcel Dekker, Inc.

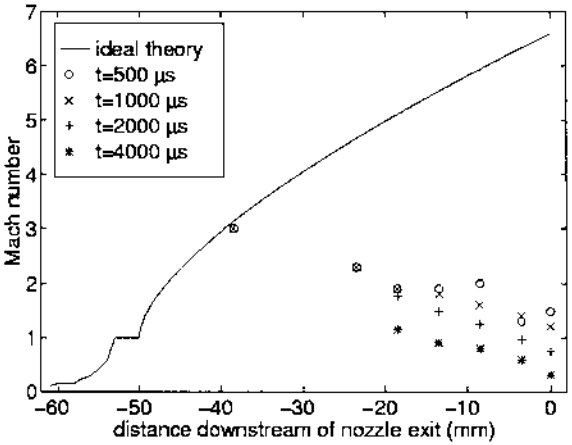


Figure 4 Experimental and ideal axial Mach number within the PowderJect dermal device [4]. These profiles are provided after the starting process.

In the first image, 21 μs after diaphragm rupture (Fig. 5a) the density change designating a shock can be seen just within the left field of view. In the next image (42 μs after diaphragm rupture, Fig. 5b) the primary shock is followed by the interface and an oblique shock front. At this point in time, the oblique shock, which represents the termination point of the starting process, has not induced flow separation. In the next 90 μs the primary shock has exited the nozzle and an oblique shock structure is present within the nozzle divergence. The remaining images at 243 μs and 354 μs after membrane rupture indicate a similar, shock-induced gas flow within which a large fraction of the particle payload is entrained.

The effect of the gas jet on entraining and accelerating a 1-mg payload of 4.7-μm polystyrene spheres (simulating a drug payload) is illustrated with two instantaneous velocity field maps, measured using time-resolved DGV (Fig. 6). The results reveal two distinct types of behavior in the particle cloud. The leading particles are delivered in a wide cloud at a typical velocity of 200–400 m/s. A narrower, quasi-steady stream of particles follows the leading cloud at 650–800 m/s.

V. APPLICATIONS

A. The PowderJect System and Drug Delivery

In the 2000 annual report of PowderJect Pharmaceuticals Plc, it was stated that two drugs were in phase II clinical trials, two more were in phase I clinical trials,

Copyright © 2003 Marcel Dekker, Inc.

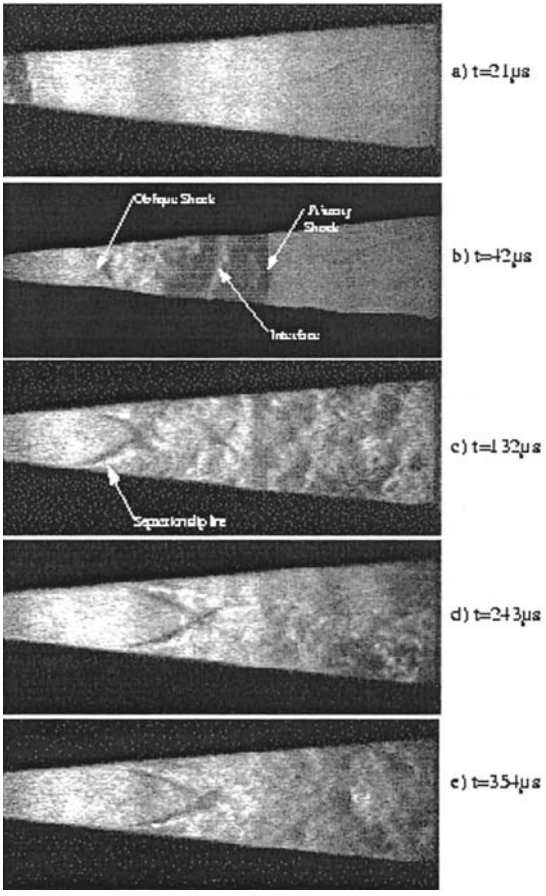


Figure 5 Schlieren images within the square-section nozzle analogous to the dermal PowderJect prototype at different time intervals after diaphragm rupture [4]. There is no particle payload in these conditions.

and six more were in preclinical trials. The first product will be lidocaine dermal, to achieve rapid onset of local anesthesia before introduction of a needle or catheter.

The drug pipeline is summarized in Figure 7.

B. The PowderJect System and Vaccine Delivery

PowderJect Pharmaceuticals (2000 annual report) have used the dermal PowderJect device to deliver conventional vaccines, formulated in dry powder form

Copyright © 2003 Marcel Dekker, Inc.

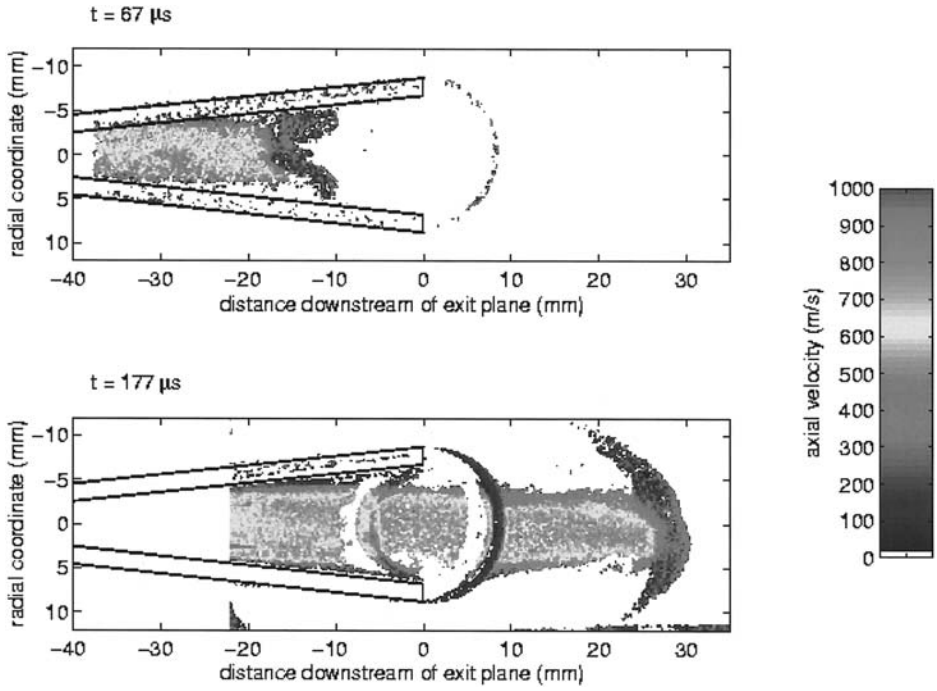

t = 67 μs
radial coordinate (mm)
distance downstream of exit plane (mm)
t = 177 μs
radial coordinate (mm)
distance downstream of exit plane (mm)
axial velocity (m/s)

Figure 6 DGV measurements of the instantaneous particle velocity field inflow from a prototype dermal PowderJect device at 67 μs and 177 μs after diaphragm rupture [12]. The model drug particle payload is 1 mg of 4.7-μm polystyrene spheres. (See color insert.)

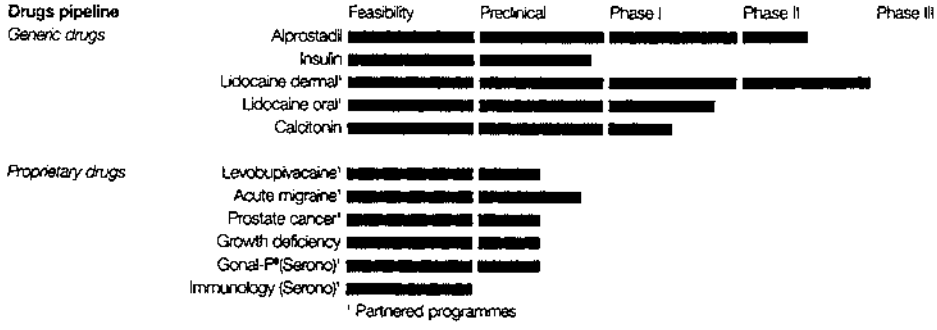


Figure 7 PowderJect Pharmaceuticals Plc drugs pipeline.

Copyright © 2003 Marcel Dekker, Inc.

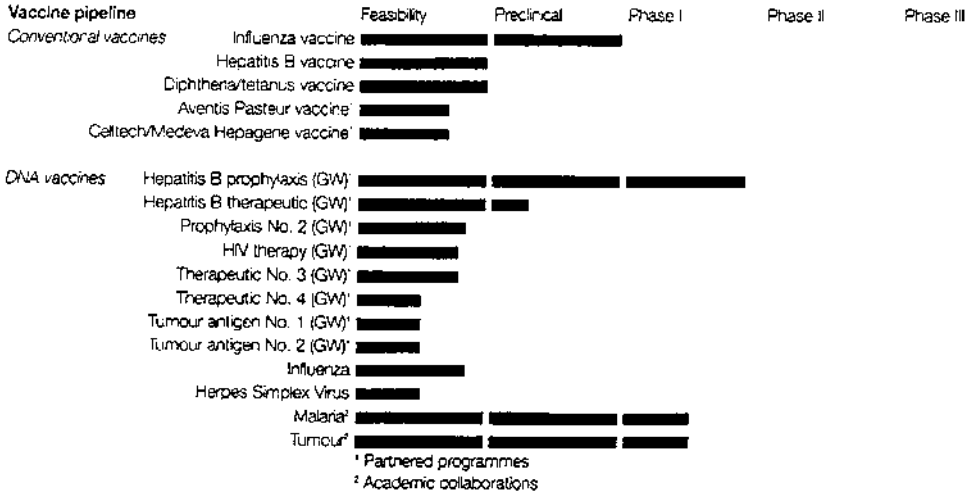


Figure 8 PowderJect Pharmaceuticals Plc vaccines pipeline.

and DNA vaccines, coated onto gold particles in feasibility and preclinical experiments. A genetic hepatitis B vaccine has produced very promising results in a phase 1 clinical trial. Two other DNA vaccines are in phase I clinical trials (malaria, tumor).

The vaccines pipeline is summarized in Figure 8.

VI. FUTURE DIRECTIONS AND CONCLUSION

Our long-term aim is to increase the mass of drug delivered transdermally, and to deliver it to a chosen layer of skin. This requires the formulation of drug particles of carefully controlled size and density that are sufficiently robust to remain intact after impact with the skin. Also required is the design of compact devices that deliver drug particles at uniform velocity, to a target diameter of 10 mm or more, with uniform spatial distribution. Progress in this direction was reported recently by Kendall et al. [8], who described a contoured shock tube (with a parallel driver section, a membrane cassette, and a contoured divergent section downstream) that was configured to deliver particles to the target skin with a narrow and controlled velocity distribution and a uniform spatial distribution. Developments such as these in device design and particle formulation will improve dose accuracy and the range of drugs that can be delivered by this needle-free and painless method.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. JC Sanford, MT Klein. Delivery of substances into cells and tissues using a particle bombardment process. Particulate Sci Tech 5:27–37, 1987.
2. BJ Bellhouse, DF Sarphie, CJ Greenford. Needle-less syringe using gas flow for particle delivery. International patent WO 94 24263, 1994.
3. NJ Quinlan, MAF Kendall, BJ Bellhouse, RW Ainsworth. Investigations of gas and particle dynamics in first generation needle-free drug delivery systems. International Journal on Shock Waves, 10(6):395–404, Jan. 2001.
4. MAF Kendall, NJ Quinlan, SJ Thorpe, RW Ainsworth, BJ Bellhouse. The gas-particle dynamics of a high-speed needle-free drug delivery system. In: GJ Ball, R Hillier, GT Roberts, eds. Shock Waves. Southampton, UK: University of Southampton, 1999, pp. 605–610.
5. TL Burkoth, BJ Bellhouse, G Hewson, DJ Longridge, AG Muddle, DF Sarphie. Transdermal and transmucosal powdered drug delivery. Crit Rev Ther Drug Carr Syst 16:331–384, 1999.
6. MAF Kendall, PJ Wrighton-Smith, BJ Bellhouse. Transdermal ballistic delivery of micro-particles: Investigation into skin penetration. World Congress of Medical Physics and Biomedical Engineering, Chicago, IEEE 0-7803-6568-6/00, 2000.
7. BJ Bellhouse, NJ Quinlan, RW Ainsworth. Needle-less delivery of drugs, in dry powder form, using shock waves and supersonic flow. International Symposium on Shock Waves, Australia, 1997, pp. 51–56.
8. MAF Kendall. The delivery of particulate vaccines and drugs to human skin with a practical, hand-held shock tube-based system. Shock Waves Journal, 12(1), pp. 22–30, July 2002.
9. JF Meyers. Development of Doppler global velocimetry as a flow diagnostics tool. Measurement Sci Tech 6:769–783, 1995.
10. RW Ainsworth, SJ Thorpe, RJ Manners. A new approach to flow field measurement—a view of Doppler global velocimetry techniques. J Heat Fluid Flow 18:116–130, 1997.
11. NJ Quinlan, RW Ainsworth, BJ Bellhouse, RJ Manners, SJ Thorpe. Application of Doppler global velocimetry to supersonic gas-particle flows in drug delivery. In: B Ruck, A Leder, D Dopheide, eds. Laser Aneometry Advances and Applications. Karlsruhe, Germany: GALA, e.V, 1999, pp. 629–636.
12. NJ Quinlan. Gas and particle dynamics in transdermal powdered drug delivery. DPhil thesis, Department of Engineering Science, University of Oxford, UK, 1999.

Copyright © 2003 Marcel Dekker, Inc.

51

Intraject: Prefilled, Disposable, Needle-Free Injection of Liquid Drugs and Vaccines

Adam Levy
Weston Medical Group plc, Trumpington, England

I. INTRODUCTION

A. Intraject

Intraject is a prefilled, disposable device for the needlefree subcutaneous injection of liquid drugs and vaccines (Fig. 1). Intraject is greatly preferred by patients to needle and syringe injection, and is replacing both prefilled syringes and auto-injectors in many commercial product areas. The list of these product areas and the companies licensing Intraject (Table 1) reflects the growing demand for this technology. This demand is fueled by a growing concern over the extent and risk of needlestick injuries, the highly competitive and genomics-driven biotechnology pipeline that is increasingly developing injectable drugs, and a trend toward long-term administration of these drugs in the home setting.

B. Weston Medical Group plc

Intraject has been developed by Weston Medical Group plc, a pioneering British-based drug delivery company. The company was established in 1994, has headquarters in Cambridge and development facilities in Stradbroke, Suffolk, and currently employs around 130 people. In May 2000, it completed the largest ever Chapter 20 (scientific-research-based companies) listing on the London Stock Exchange, raising £52.5 million (before expenses).

Copyright © 2003 Marcel Dekker, Inc.

Figure 1 The Intraject needle-free injection device developed by Weston Medical Group plc. (See color insert.)

The Intraject technology is proprietary to Weston Medical and is protected by over 140 patents. The business strategy of Weston Medical is to license Intraject exclusively to pharmaceutical and biotechnology companies for specific therapeutic, product, and geographic territories, in exchange for upfront, milestone, and royalty payments. Intraject is applicable to a wide range of both marketed and development-stage injectable drugs, including therapeutic proteins and peptides, monoclonal antibodies, small-molecule-based drugs, and vaccines.

This chapter reviews the technical design of the Intraject system, and the preclinical and clinical data that have been generated with the device. It describes the position of Intraject within the available range of drug delivery approaches, and establishes that Intraject represents a uniquely low-risk, high-return drug delivery proposition.

II. HISTORICAL DEVELOPMENT

Needle-free injection was first described by Marshall Lockhart in 1936 after the observation that high-pressure jets of hydraulic oil could pierce the skin [1]. In the early 1940s Hingson and others developed high-pressure "guns" using a very fine jet of liquid medicine to pierce the skin and deposit drug into the underlying tissue [2]. Such devices were used extensively to inoculate soldiers against infectious disease, and were later applied more widely in large-scale vaccination programs [3]. However, owing to the reusable nature of the devices, and the inherent risk of cross-contamination, there was a sharp decline in their usage.

Although needle-free devices have since been developed for the delivery of drugs such as insulin and human growth hormone, they required users to go through a series of intricate steps to load the drug into the device prior to injection. As a result, market penetration and acceptance were poor, and the need for a safe and easy-to-use needle-free injection system still remained.

Intraject overcomes both the safety risks associated with early needle-free devices and the user difficulties associated with the more recent needle-free systems. The key is that Intraject is prefilled and disposable and this enables it to meet the needs of patients, practitioners, and pharmaceutical companies.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Intraject Current Partnering Agreements

Partner	Drug	Indication	Current sales of drug by partner
Roche	Pegasys	Hepatitis B, C, and cancer	Filed with FDA and EMEA; approved in Switzerland
GlaxoSmithKline	Sumatriptan	Migraine	$1.1 billion
Pharmacia Corporation	Fragmin	Anticoagulation therapy	$213 million
Cambridge Antibody Technology	In-house and partnered antibodies	Various	Various stages of development
Japanese Pharmaceutical company	Undisclosed	Undisclosed	Undisclosed
Abbott Laboratories	Undisclosed 11 targets	Various	Various clinical and preclinical candidates
Chugai Pharmaceuticals	Undisclosed	Undisclosed	Undisclosed

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Key Market Drivers Within the Drug Delivery Value Chain

Pharmaceutical drivers	Health care professional drivers	Patient drivers
Lifecycle management	Risk of needlestick injury	Increased role in decision making
Product differentiation	Needle stick legislation	Overwhelmingly needle-averse
Market penetration	Focus on patient compliance	Emphasis on expanded freedom
Research and development competition; new injectable products	Medicoeconomic power	DTC advertising

III. MARKET DRIVERS

The market for needle-free drug delivery is shaped by a number of forces that act on patients, health care professionals, and ultimately, pharmaceutical companies (Table 2). These forces are driving pharmaceutical companies to explore novel drug delivery options both for the differentiation of existing and new products, and for the expansion of, and penetration into, target patient groups.

In parallel, however, rising research and development costs and an increasing urgency in the time lines for drug development are presenting resistance to the uptake of innovative new drug delivery programs, the thinking being that such steps would increase both the risk and time line for drug development. The key advantages of the Intraject system, particularly in reference to the market forces described above, are shown in Table 3.

IV. INTRAJECT: THE TECHNOLOGY

A. How to Use Intraject

Intraject has been designed with ease of use as a prime consideration. A single-use self-injection can be carried out in less than 5 s by following three straightforward steps, as shown in Figure 2. Intraject is suitable for patient self-administration at home with minimum training needed.

B. How Intraject Works

Intraject uses a compact nitrogen gas source to propel a premeasured quantity of liquid medicine through the skin and into the underlying subcutaneous tissue, without the use of a needle. As shown in Figure 3, the device is composed of

Copyright © 2003 Marcel Dekker, Inc.

Table 3 Key Advantages of the Intraject Needlefree Injection Device

Established principle: Over two million needlefree injections have been performed. This established long-term safety profile is in sharp contrast to the higher-"technology" drug delivery approaches, which are only now emerging into clinical trials, and which present a high technical and regulatory uncertainty.

Patient orientation: Studies have demonstrated that Intraject is greatly preferred by patients to needle-and-syringe injection. The device permits simple, pain-free self-injection by patients, with minimal training. Injection takes less than 5 s.

No drug reformulation: Liquid needle-free injection does not demand the high-risk, high-cost reformulation required by other approaches, such as inhalation, powder injection, or oral delivery. Drugs are not modified by injection with Intraject, and delivery is bioequivalent to conventional needle and syringe.

Simple regulatory path: The regulatory route for Intraject is simple, and does not necessarily involve full phase I–III clinical trials. The two regulatory requirements for approval of a product are drug stability in the device and pharmacokinetic equivalence to the approved delivery (i.e., needle and syringe). These present minimal risk—Intraject drug contact materials are standard pharmaceutical materials, and bioequivalence has been demonstrated for a number of different drugs. The clinical trial program is unchanged for a product in development.

Low cost: Intraject represents a low-cost drug delivery approach. Cost of goods is minimized as devices are simple and are designed for manufacture, and bioavailability is the same as that with a needle and syringe. Also the product overfill is much lower than with conventional vials. Reformulation is not required, so significant savings are made on research and development and product sale revenues are brought forward by the rapid time to market.

Established manufacture: Manufacture represents a key risk for pharmaceutical companies evaluating novel drug delivery systems. A commercial-scale Intraject manufacturing process is on target for full operation by the end of 2002.

Figure 2 How to use Intraject. There are three steps to using the Intraject device. In the first step, a plastic tip is snapped off, exposing the orifice in the device. In the second step, a band is removed that is designed to permit actuation of the device but prevent accidental activation. Once this safety band is removed, a light, but continual pressure of the device on to the skin will allow the device to actuate. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

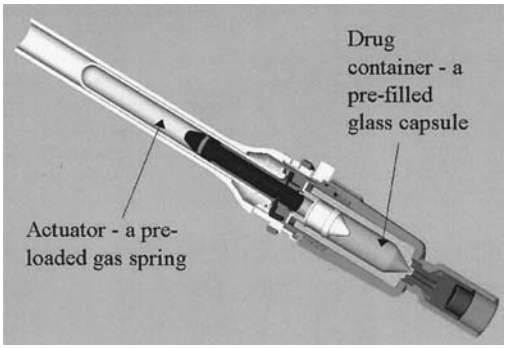


Figure 3 Cross section of Intraject. Intraject consists of two parts. The actuator provides a power source and is not in contact with the drug. The drug capsule is assembled from standard-grade pharmaceutical materials. (See color insert.)

two main parts: an actuator, which contains a preloaded gas spring-and-trigger mechanism, and a capsule, which is an aseptically assembled drug container.

Drug contact materials within the device are all standard pharmaceutical-grade materials, ensuring simple low-risk drug stability and rapid clinical development. The device release mechanism is safe, simple, and reliable, and prevents injection until optimum contact pressure between the nozzle and the skin is achieved. Once used, the device contains no residual energy.

V. INTRAJECT: PRECLINICAL AND CLINICAL EVALUATION

A. Preclinical Studies

The Intraject configuration is optimized to create a well-understood and characterized injection pressure profile (Fig. 4). Delivery does not alter drug product, and a series of in vitro studies has shown that even large complex, multisubunit drugs such as monoclonal antibodies are not modified during high-pressure injection (Fig. 5). As discussed later, this is a key element in the low-risk profile of the technology, allowing pharmaceutical partners to use existing liquid drugs with no need to reformulate.

B. Clinical Studies

1. Imaging

Advanced magnetic resonance imaging (Fig. 6) has demonstrated that Intraject delivers reliable subcutaneous injections. Around 99% of patients from a wide

Copyright © 2003 Marcel Dekker, Inc.

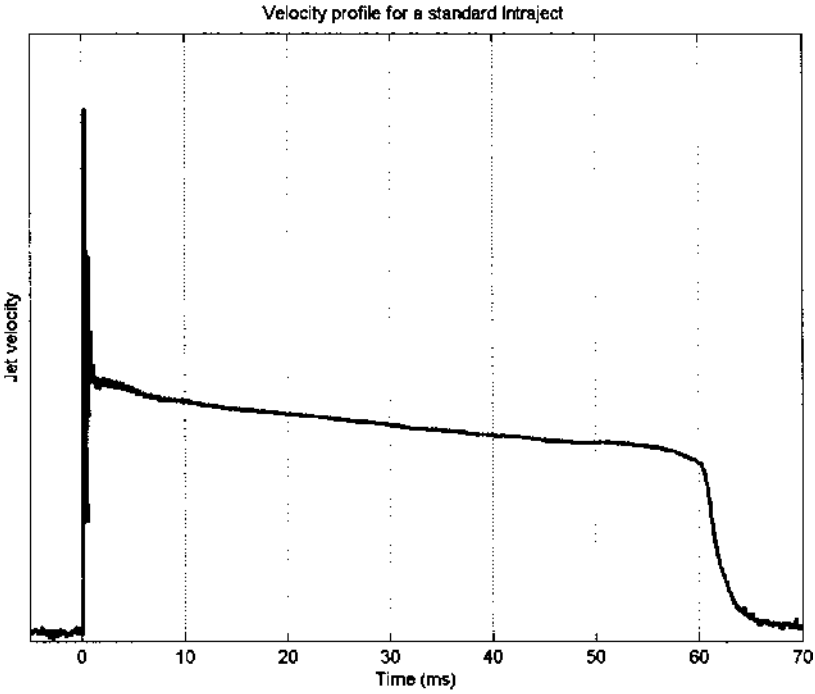


Figure 4 Pressure profile created by Intraject. The unique pressure profile of the Intraject device is a result of the way that energy is packaged within the device and delivered. Drug is delivered during the low-pressure level, and changes in drug properties, including the binding properties of monoclonal antibodies, are not observed after injection with the device.

range of ages, ethnic origins, and in both sexes receive a suitable subcutaneous injection.

2. Pharmacokinetics

Subcutaneous delivery with Intraject is bioequivalent to that with a needle and syringe. This has been consistently shown in a series of preclinical and clinical pharmacokinetic experiments, with a range of drugs from small molecules to proteins [4] and monoclonal antibodies (Fig. 7). These studies involve standard liquid products, and no formulation or dosage change is required. The result of this pharmacokinetic profile is that Intraject takes advantage of a rapid low-risk path through regulation that does not involve large or protracted efficacy trials.

Copyright © 2003 Marcel Dekker, Inc.

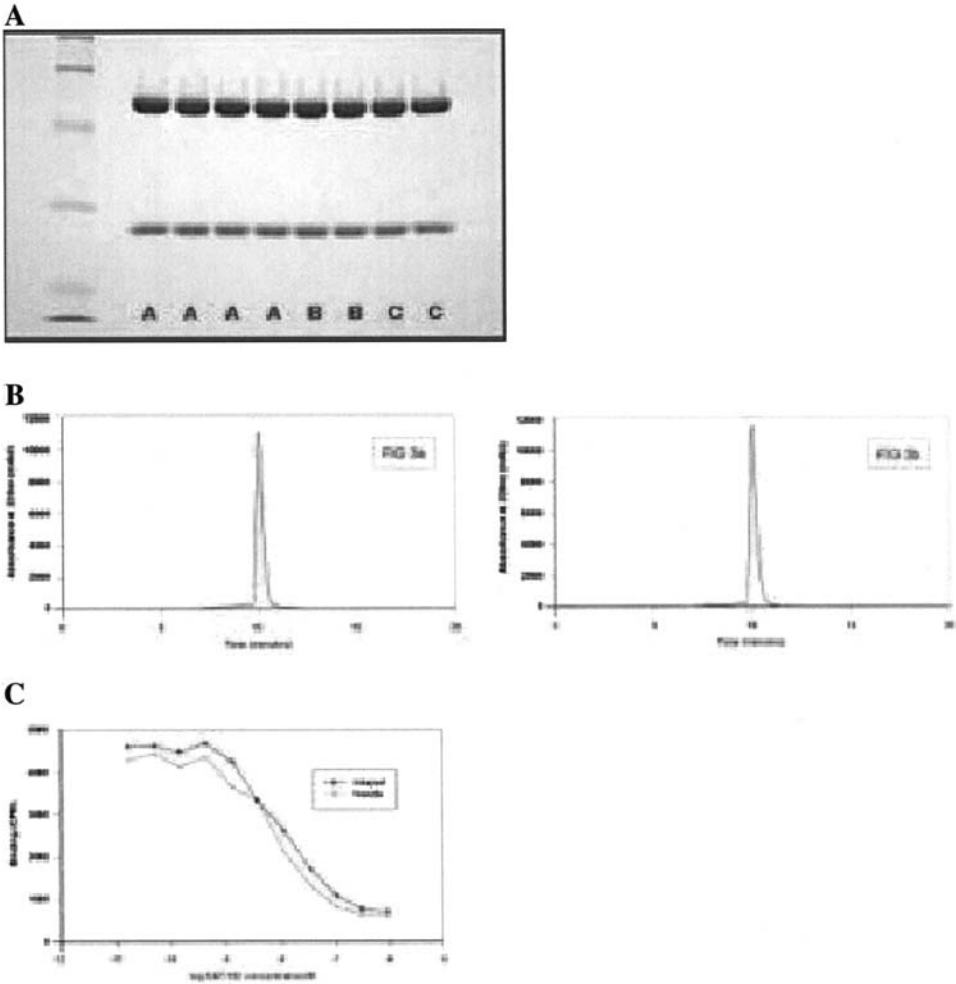


Figure 5 In vitro comparison of monoclonal antibody delivered by Intraject and by needle and syringe. Because of its pressure profile, Intraject delivery does not alter the properties of injected products. This is part of the way in which this technology represents a low risk to pharmaceutical companies adopting novel drug delivery. This work was conducted by Cambridge Antibody Technology with CAT-192, a proprietary human monoclonal antibody candidate. (A) Analysis of CAT-192 by reducing SDS-Page after injection through (A) Intraject, (B) conventional needle and syringe, and (C) control antibody (no injection). (B) Analysis of CAT-192 by reducing gel permeation HPLC after injection through (A) Intraject and (B) a conventional needle-and-syringe. (C) Analysis of CAT-192 by TGF-beta-1 binding after injection through Intraject and conventional needle and syringe. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

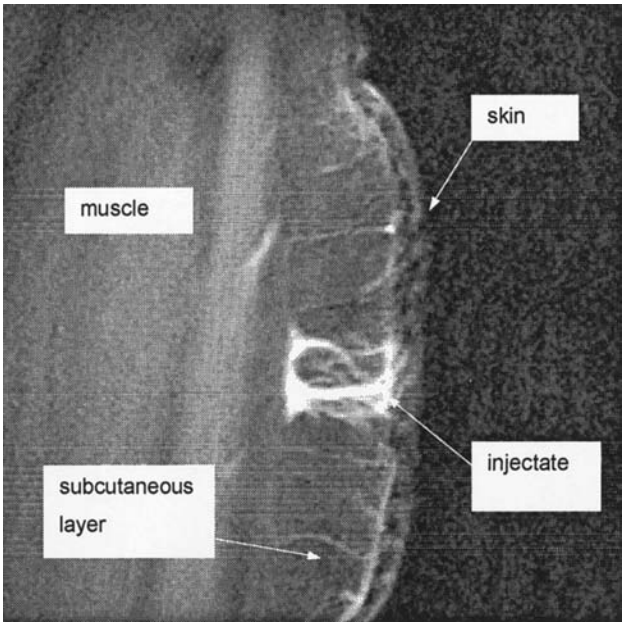


Figure 6 MRI scan following injection with Intraject into a patient's abdomen. Injectate, seen in white, appears to reflect back from the fascia overlying the muscle. Because of the pressure profile created by the device, injectate is retained within the subcutaneous layer, even in very thin patients, and Intraject delivers a reliable subcutaneous injection.

3. Patient Preference

Intraject has been found to be overwhelmingly preferred by patients to conventional needle-and-syringe injection. In a volunteer study (so not a needle-averse population), in which injections were practitioner-administered (so not self-injection), Intraject was favored by over 80% of subjects. This result has been confirmed in all studies with a patient preference element. This finding is further supported by marketing data, in which a spontaneous switching rate of over 80% was seen from a needle-containing device to Intraject. This finding additionally supports a market-switching rate of 98% to Intraject.

Intraject has also been shown to have a lower incidence of bruising than that found with conventional needle-and-syringe injection, even when delivered by an experienced clinician. In long-term follow-up of volunteers, there is no evidence of any differences, such as scarring, between Intraject and needle and syringe.

Copyright © 2003 Marcel Dekker, Inc.

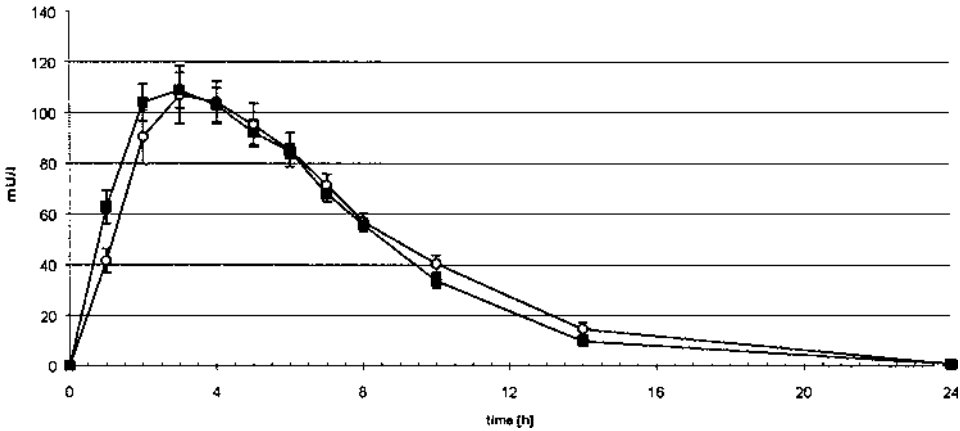


Figure 7 Pharmacokinetic profile of growth hormone delivered with Intraject and with a conventional needle and syringe. Needle-free delivery with Intraject (closed square) is bioequivalent to that with needle and syringe (open circle). T_{max} is marginally shorter for Intraject than with a needle and syringe (although well within regulatory requirements) and intrapatient variation is reduced. This is attributable to the repeatable mechanical nature of Intraject, rather than the error-prone and variable needle-and-syringe injection.

VI. MANUFACTURING STRATEGY

Weston Medical is applying a "virtual factory" concept and to this end has created and manages a cost-effective and fully integrated third-party supply chain capable of providing a range of manufacturing options to its licensees. Weston Medical currently has a capacity of 2 million Intraject units per year for stability and clinical trials. A commercial-scale manufacturing operation, capable of producing 20 million Intraject units per annum, will be in place by the end of 2002. Weston has secured a number of key manufacturing suppliers to support its virtual factory. This includes Munnerstadter Glaswarenfabrik GmbH in Germany to produce Weston Medical's proprietary glass capsule subcomponent and Patheon UK Ltd for commercial-scale drug filling and device assembly.

To meet the needs of both its large pharmaceutical and smaller biotechnology partners, Weston Medical operates a cost-effective, yet highly flexible manufacturing approach. Larger partners, particularly those with device experience, may elect to perform assembly and fill of Intraject in-house. This entire process can also be outsourced, and Weston has worked with its manufacturing partners to secure this turnkey option for its licensees. A third solution is to outsource device assembly and for licensees to take filling equipment in-house. This route

Copyright © 2003 Marcel Dekker, Inc.

is particularly attractive for biotechnology partners, who can outsource device assembly, while retaining control over critical biological products.

VII. REGULATORY APPROVAL

As a prefilled device, Intraject is regulated as a medicinal product in the European Union (EU) and in the United States (U.S.). The responsibility for obtaining regulatory approval for the Intraject-drug combination lies with Weston Medical's licensees, and Weston Medical works closely with its licensees to agree to an appropriate regulatory strategy and provide them with the relevant device aspects of the approval process. Formal discussions have been held with EU, U.S., and Japanese regulators, and development plans have been submitted.

For the use of marketed products in Intraject, regulatory submissions will include simple bioequivalence and stability drug studies. As has been discussed, these present a low technical risk owing to the materials from which Intraject is manufactured, and the way that drug is delivered. Intraject is also becoming increasingly integrated into early clinical studies with novel developmental compounds. Broadly, Intraject is included as an arm in a phase II trial, followed by pivotal phase III studies.

VIII. RISK AND RETURN IN DRUG DELIVERY

With its innovative simple design, and its market orientation, Intraject fills a unique position in the spectrum of drug delivery technologies. Intraject is a highly patient-oriented, exclusive device that meets the needs of patients, health care professionals, and pharmaceutical and biotechnology companies, but presents minimal product risk. This is in contrast to several other drug delivery technologies, which can be considered with regard to their relative risk-return profile as shown in Table 4 and Figure 8. Compared to alternative delivery approaches, Intraject offers a high market return at minimal risk to drug development.

IX. FUTURE DIRECTIONS

Intraject is a uniquely positioned technology—it is low risk, yet it is oriented to market needs. Second-generation devices are also in development, working from the Intraject platform, as shown in Figure 9. This portfolio of developmental devices has been selected to expand the range of drugs that can be administered

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Relative Risk and Return of Various Drug Delivery Approaches

Drug delivery mode	Market return	Technical risk
Oral delivery of macromolecules	High Patient oriented, strong compliance, and product differentiation High development costs	Very high Extremely high formulation risk Poor bioavailability
Inhalation	Medium Less patient oriented than oral delivery, but established delivery approach High cost of goods owing to poor bioavailability	High High formulation risk, uncertain long-term acceptability Poor bioavailability
Intraject	Medium Preferred by patients, exclusive and unique delivery approach	Low Standard materials and simple design Bioeqiuvalent delivery and simple low-risk regulatory path Manufacturing on track
Nonprefilled needle-free devices	Low Nonexclusive business model, cumbersome and poorly patient-oriented	Very low Established nonprefilled device with 510k/CE marking

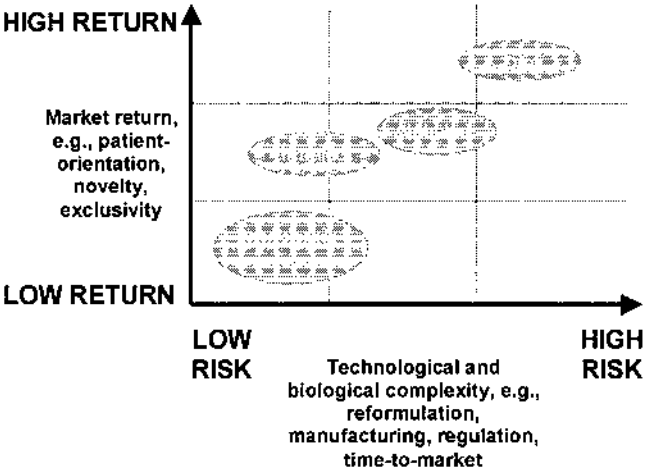


Figure 8 Graphic representation of risk and return in the spectrum of drug delivery approaches.

Copyright © 2003 Marcel Dekker, Inc.

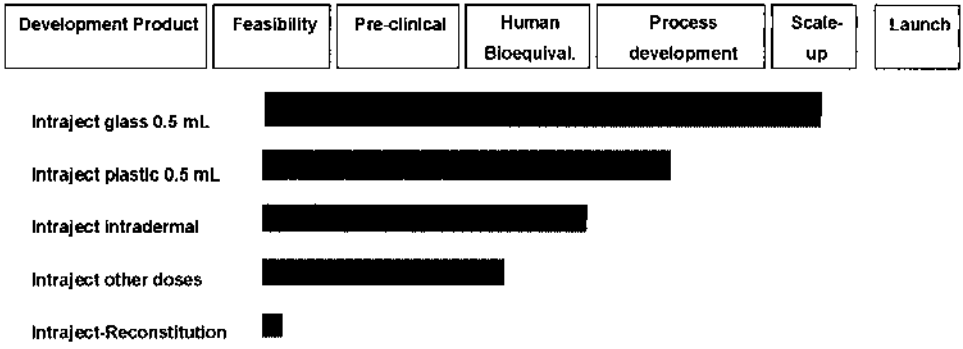


Figure 9 The Intraject product pipeline.

with Intraject through decreased device cost, expanded injection volume range, and widened drug formulation and site of injection.

X. SUMMARY

This chapter has presented the Intraject needle-free injection technology developed by Weston Medical Group. Intraject is uniquely positioned to respond to the growing, and as yet unmet, need for a novel market-oriented drug delivery approach that conveys minimal technical risk and does not extend product development time lines. This is increasingly being recognized by the pharmaceutical and biotechnology industries, reflected in the growing list of companies licensing the Intraject technology.

REFERENCES

1. ML Lockhart. Hypodermic injector. US Patent Office serial number 69,199, 1936.
2. RA Hingson, JG Hughes. Clinical studies with jet injection: a new method of drug administration. Anaesth Analg 26:221–230, 1947.
3. RA Hingson, SD Hamilton, M Rosen. The historical development of jet injection and envisioned uses in mass immunization and mass therapy based upon two decades' experience. Milit Med 128:516–524, 1963.
4. S de la Motte, J Klinger, G Kefer, T King, F Harrison. Pharmacokinetics of human growth hormone administered subcutaneously with two different injection systems. Arzneimittelforschung 51:613–617, 2001.

Copyright © 2003 Marcel Dekker, Inc.

52
Implants and Injectables

Franklin W. Okumu and Jeffrey L. Cleland*
Genentech, Inc., South San Francisco, California, U.S.A.

I. INTRODUCTION

When considering new options for drug delivery, the most direct approach is usually parenteral administration. Because many in vivo preclinical research studies and early clinical trials are performed by direct injection, such as intravenous (IV), intramuscular (IM), or subcutaneous (SC) administration, the development of injectable controlled-release dosage forms is more likely to succeed commercially than alternative routes of delivery (oral, topical, pulmonary), assuming that these dosage forms provide the desired efficacy and safety [1]. The ability of controlled-release dosage forms to modulate the systemic or local persistence of a given drug may significantly alter the efficacy or safety of the drug compound. In the case where the active compound has a short half-life in vivo, a modified-release system can extend exposure after a single administration (Table 1). By extending the drug exposure time, these systems significantly reduce the number of injections a patient must receive to control his condition. Another potential benefit of these types of systems is the ability to administer high doses of drug per injection with a lower maximum serum concentration (C_{max}) than a bolus injection. In some cases, the C_{max} from the controlled-release preparation may be lower than that achieved with the more frequent bolus drug administration typically used for treatment, thus avoiding any undesired side effects that may be associated with a high C_{max}. In this section, we will discuss examples of modified-release systems that are injected or implanted in the body where they then deliver a controlled release of the drug. Four classes of modified-release systems are reviewed: implants, microspheres, injectable gels, and nanospheres (liposomes).

**Current affiliation*: Targesome, Inc., Palo Alto, California, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Injectable and Implantable Modified-Release Systems

Class	Delivery matrix	Therapeutic agent	Duration (weeks)	Ref.
Implant (surgically inserted)	Osmotic pump, collagen, PLGA	Leuprolide, sufentanil, rhBMP, rhNGF	12–52	[2–4]
Implant (injected with large needle)	PLGA, collagen	Leuprolide, GHRP-1, TNF-R, calcium phosphate	1–24	[5–8]
Microsphere	PLGA, POE, PEG-lactide, collagen	Leuprolide, rhGH, GHRP-1, rhNGF, rhVEGF	1–12	[4,9–11]
Injectable gels	PLA, PLGA, PEG-PLGA	Taxol, leuprolide, rhGH, rhVEGF, deslorelin	1–24	[15–18]
Nanosphere (liposomes)	PEG-PLGA, lipids, PLGA	Doxorubicin, lactoferrin	0.5–1	[19–21]

II. IMPLANTS

Typically, implants require the use of large-gauge needles or surgical procedures for administration. Therefore, a longer duration (>3 months) of drug release is required for patient acceptability, avoiding the need for frequent invasive procedures. Because implants contain a fixed dose of drug in a fixed volume (implant size), they do not have utility in the treatment of diseases requiring drug dosing based on weight (mg/kg) or body surface area (mg/m^2) with the possible exception of a patient population that has a narrow weight or body surface area distribution. The advantage of implantable devices is that they may operate for long periods of time once implanted and provide a more controlled release than injectable systems. For this reason implants are generally considered when the therapeutic window (range of safe and efficacious doses) is sufficient to allow fixed doses, which will yield varying serum levels of the drug depending upon the patient weight, and chronic administration of drug is required. The functional lifetime of each implant is controlled by the amount of drug contained in the reservoir (volume $<$ 2.0 mL) and the delivery rate (controlled by the implant). One drug that meets the dosing requirements for implants is leuprolide acetate, which is used in the treatment of prostate cancer, endometriosis, and precocious puberty. Recently, a titanium osmotic pump, Duros (Alza Corporation), has been developed for the sustained delivery of leuprolide acetate to treat prostate cancer.

Copyright © 2003 Marcel Dekker, Inc.

For this system, a continuous drug dose is delivered over a 12-month period providing patient convenience and compliance. Further, this type of implant may be easily removed to halt drug exposure if required.

Another approach for sustained delivery of leuprolide acetate and other luteinizing hormone–release hormone (LH-RH) agonists or antagonists is the use of biodegradable implants. Biodegradable implants offer the advantage of a single procedure (no removal). Zoladex (AstraZeneca), a PLGA goserelin acetate implant, is injected subcutaneously with a 16-gauge needle to provide sustained release of goserelin for 28 days.

The choice of matrix used for these biodegradable systems depends on a number of factors such as the physicochemical properties of the entrapped drug, the desired duration of release (>3 months), acute (wound healing) or chronic (growth factors, hormones) administration, and regulatory status. The U.S. Food and Drug Administration has generally allowed clinical investigation of delivery systems based on matrix platforms that have been extensively used for biomedical and pharmaceutical applications [e.g., poly(lactide-coglycolic acid) (PLGA), poly(lactic acid) (PLA), collagen, etc.]. New materials or materials in use in the food industry can also be used as delivery matrices after sufficient preclinical toxicology studies have been conducted. These studies would evaluate the metabolism of the matrix and its degradation products as well as the overall biocompatibility of the system. Pilot toxicology studies of the biodegradable matrix should routinely be performed prior to development of any injectable matrix for parenteral delivery to assure that the matrix itself has adequate safety for human use.

III. INJECTABLE MODIFIED-RELEASE SYSTEMS

Unlike implants, injectable modified-release dosage forms may be administered more frequently (e.g., <1/month), but still require biocompatibility assessments for matrices that consist of new biomaterials. Because these dosage forms are not easily removed, a biodegradable matrix is required. Examples of these matrices include biodegradable polymers (e.g., PLGA) [4,9–11], natural compounds (e.g., collagen) [6], and liposomal preparations [19–21]. Usually, the matrix is fabricated into an easily injectable (small needle size; 20–30 G) form for administration at the desired tissue site (e.g., subcutaneously). The dosage form may be either a solid, gel, or liquid. Solid dosage forms such as biodegradable microspheres consisting of PLGA have been used as an injectable depot delivery system of small-molecule drugs, peptides, and proteins [9–11]. These systems require aseptic manufacturing processes and a suspension vehicle to allow injection of the microspheres. In contrast, gel and liquid forms may be prepared with terminal filter sterilization and have generally fewer manufacturing steps than micro-

Copyright © 2003 Marcel Dekker, Inc.

spheres [12–18]. The injectable gels usually consist of a solvent to dissolve the matrix and/or the therapeutic agent and they form an "implant-like" depot upon injection. Because the volume of injection affects the size of the depot formed from these gels, the rate of drug release may change as a function of dose or dose concentration. This dosing difficulty may be overcome by systems that minimize the initial release from the depot surface. These systems are at an early stage of development and require more extensive preclinical and clinical studies to evaluate their potential as modified-release dosage forms.

The injectable dosage forms discussed above are utilized for parenteral injection to various tissues in the body (e.g., subcutaneously), but are not used for intravenous administration owing to their size (microspheres) or properties (gels). For intravenous administration, biodegradable nanospheres and liposomes are generally used. These systems modify the release of entrapped drug as they circulate through the body or accumulate at a specific targeted site of action (e.g., tumor, organ, blood, etc.). For example, the accumulation of liposomes containing a chemotherapeutic agent such as doxorubicin occurs in solid tumors, providing a high local drug concentration and minimizing systemic exposure [19]. The circulation time of nanoparticles is dependent upon the recognition by the body and their size, wherein particles that have a surface that binds serum proteins (opsinization) and/or are larger than 100 nm are cleared rapidly through phagocytic pathways. Liposomes containing PEG lipids are protected from serum protein binding and phagocytic recognition yielding a longer circulating half-life than conventional liposomes. In general, these systems allow for weekly administration and provide a method for improving the safety and efficacy of potentially toxic small-molecule therapeutics.

IV. CONCLUSION

Currently, a pharmaceutical scientist has a variety of options for modified-release drug delivery of therapeutic agents. The proper selection of a modified-release dosage form is dependent upon several factors including the physicochemical properties of the drug, the drug pharmacology, and the disease indications [1]. Typically, modified-release delivery systems are developed after the bolus injection form (not controlled release) of the drug has been assessed in clinical trials. However, with the discovery of more potent drugs such as growth factors and kinase inhibitors, modified-release formulations may be necessary prior to human clinical trials and/or commercialization. These systems also offer significant advantages to patients by reducing dosing frequency (increasing compliance) and possibly improving the drug's safety profile through lower C_{max} levels than a bolus injection. This section covers recent developments in implantable or injectable modified-release systems.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. J Cleland, A Daugherty, R Mrsny. Emerging protein delivery methods. Curr Opin Biotech 12:212–219, 2001.
2. M Higaki, Y Azechi, T Takase, R Igarashi, S Nagahara, A Sano, K Fujioka, N Nakagawa, C Aizawa, Y Mizushima. Collagen minipellet as a controlled release delivery system for tetanus and diphtheria toxoid. Vaccine 19(23–24):3091–3096, 2001.
3. S Itoh, M Kikuchi, K Takakuda, Y Koyama, HN Matsumoto, S Ichinose, J Tanaka, T Kawauchi, K Shinomiya. The biocompatibility and osteoconductive activity of a novel hydroxyapatite/collagen composite biomaterial, and its function as a carrier of rhBMP-2. J Biomed Mater Res 54:445–453, 2001.
4. WM Saltzman, MW Mak, MJ Hahoney, ET Duenas, JL Cleland. Intracranial delivery of recombinant nerve growth factor: release kinetics and protein distribution for three delivery systems. Pharm Res 16:232–240, 1999.
5. RE Eliaz, D Wallach, J Kost. Delivery of soluble tumor necrosis factor receptor from in-situ forming PLGA implants: in-vivo. Pharm Res 22:563–570, 2000.
6. CH Lee, A Singla, Y. Lee. Biomedical applications of collagen. Int J Pharm 221: 1–22, 2001.
7. P Looss, A-M Le Ray, G Grimandi, G Daculsi, C. Merle. A new injectable bone substitute combining poly(-caprolactone) microparticles with biphasic calcium phosphate granules. Biomaterials 22:2785–2794, 2001.
8. HB Ravivarapu, KL Moyer, RL Dunn. Parameters affecting the efficacy of a sustained release polymeric implant of leuprolide. Int J Pharm 194:181–191, 2000.
9. JL Cleland, OL Johnson, S Putney, AJS Jones. Recombinant human growth hormone poly(lactic-co-glycolic acid) microsphere formulation development. Adv Drug Del Rev 28:71–84, 1997.
10. YY Yang, JP Wan, TS Chung, PK Pallathadka, S Ng, J Heller. POE-PEG-POE triblock copolymeric microspheres containing protein-1: preparation and characterization. J Control Rel 75:115–128, 2001.
11. JL Cleland, ET Duenas, A Park, A Daugherty, J Kahn, J Kowalski, A Cuthbertson. Development of poly-(d,l-lactide-co-glycolide) microsphere formulations containing recombinant human vascular endothelial growth factor to promote local angiogenesis. J Control Rel 72:13–24, 2001.
12. FW Okumu, LN Dao, PJ Fielder, N Dybdal, D Brooks, S Sane, JL Cleland. Sustained delivery of human growth hormone from a novel gel system: SABER. Biomaterials, 2002. In press.
13. FW Okumu, A Daugherty, LN Dao, PJ Fielder, D Brooks, S Sane, JL Cleland. Sustained delivery of growth hormone from a novel injectable liquid, PLAD. Proc Int Symp Control Rel Bioact Mater 28:abstract #6210, 2001.
14. KJ Brodbeck, S Pushpala, AJ McHugh. Sustained release of human growth hormone from PLGA solution depots. Pharm Res 16:1825–1829, 1999.
15. A Gutowska, B Jeong, J Jasionowski. Injectable gels for tissue engineering. Anat Rec 263:342–349, 2001.

Copyright © 2003 Marcel Dekker, Inc.

16. B Jeong, YH Bae, DS Lee, SW Kim. Biodegradable block copolymers as injectable drug-delivery systems. Nature 388:860–862, 1997.
17. RR Kraeling, CR Barb, GB Rampacek, DLJ Thompson, JW Gibson, SA Sullivan, B Simon, PJ Burns. Luteinizing hormone response to controlled-release deslorelin in estradiol benzoate primed ovariectomized gilts. Theriogenology 40:1681–1689, 2000.
18. GM Zentner, R Ramesh, C Shih, JC McRea, M-H. Seo, H Oh, BG Rhee, J Mestecky, Z Moldoveanu, M Morgan, S Weitman. Biodegradable block copolymers for delivery of proteins and water-insoluble drugs. J Control Rel 72:203–215, 2001.
19. AA Gabizon, Selective tumor localization and improved theraputic index of anthracyclines encapsulated in long-circulating liposomes. Cancer Res 52:891–896, 1992.
20. M Trif, C Guillen, DM Vaughan, JM Telfer, JM Brewer, A Roseanu, JH Brock. Liposomes as possible carriers for lactoferrin in the local treatment of inflammatory diseases. Exp Biol Med 226:559–564, 2001.
21. JW Park, DB Kirpotin, K Hong, R Shalaby, Y Shao, UB Nielsen, JD Marks, D Papahadjopoulos, CC Benz. Tumor targeting using anti-her2 immunoliposomes. J Control Rel 74:95–113, 2001.

Copyright © 2003 Marcel Dekker, Inc.

53

Alzamer Depot Bioerodible Polymer Technology

Jeremy C. Wright,* Roy Bannister, Guohua Chen, and Catherine Lucas
ALZA Corporation, Mountain View, California, U.S.A.

I. INTRODUCTION

With the advent of therapeutic biomolecules produced by the biotechnology industry, the need for convenient sustained delivery of proteins and other biomolecules has greatly increased. The Alzamer® Depot™ technology was designed to offer sustained delivery of therapeutic agents, including proteins, peptides, other biomolecules, and small-molecular-weight compounds, for up to a month with minimal initial drug burst, and bioerosion of the dosage form.

The Alzamer Depot technology consists of a biodegradable polymer, a solvent, and formulated drug particles. The depot is injected subcutaneously, and drug is released by diffusion from the system while water and other biological fluids diffuse in. At the later stages of release, the polymer degrades, further contributing to drug release.

Currently available dosage forms include standard injections, microspheres, and other depot formulations. Microspheres and other depots offer sustained-release advantages over standard injections in compliance, convenience, fewer delivery peaks compared to standard injection therapy, and dose-sparing effects [1–10]. Microspheres, however, typically require complex production processes and harsh solvents that then require removal [5–14]. Solution depot formulation processes tend to be simpler, typically involving only biocompatible solvents as part of the depot platform [15–22]. In most published depot formulations to date,

* *Current affiliation*: DURECT Corporation, Cupertino, California, U.S.A.

Copyright © 2003 Marcel Dekker, Inc.

water-miscible solvents tended to migrate quickly from the depot, resulting in rapid formation of a porous structure [15,17,19,20]. Initial drug release from microspheres and these earlier-generation depot formulations tends to be rapid; up to 50% of the drug can be released upon injection [4,10,14–18].

In contrast, Alzamer Depot technology (ALZA Corporation, Mountain View, CA) uses biocompatible solvents of low water miscibility, which help control the initial drug release. In addition, this type of depot is easy to process and can be stored with the protein particles preformulated into the gel, enhancing convenience of use [21].

II. FORMULATION DEVELOPMENT

Alzamer Depot technology consists of the biodegradable polymer polylactic glycolic acid (PLGA), a biocompatible solvent of low water miscibility (e.g., benzyl benzoate), and formulated drug particles. Protein stability is maintained by isolating the drug in a solid particle. This particle is suspended in the nonaqueous polymer/solvent depot to prevent premature exposure to water. Dose release can be adjusted by varying the initial formulation and drug loading, as well as the injection volume of the preloaded syringe.

A. Solvent Choice and Phase Inversion

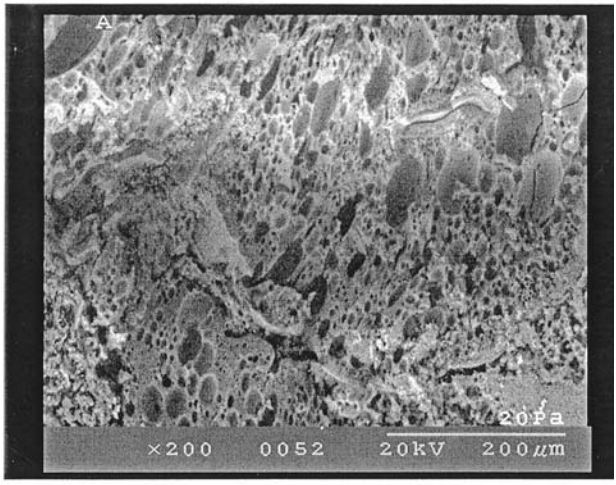
Injectable polymer/solvent depots comprising a biodegradable polymer dissolved in a biocompatible solvent transform when injected. Since the polymer is water-insoluble, contact with water in a physiological environment causes the gel to undergo phase inversion (liquid demixing), resulting in a two-phase, gelled implant [19,20]. As a result, development of the depot morphology occurs in vivo, simultaneously with release of drug, and the dynamics of phase inversion must be controlled to maintain consistent drug delivery within a specified therapeutic window.

Figure 1 shows the impact of the choice of solvent on the phase inversion process and the resultant morphology of the depot. A range of PLGAs have been tested, and the preferred polymer is a PLGA of 50/50 lactide/glycolide (L/G) ratio and a molecular weight of approximately 15,000. Figure 1A shows the morphology of a depot comprised of PLGA (L/G 50/50, M_w 16,000) and *N*-methylpyrrolidone (NMP), a solvent with relatively high water solubility. This system rapidly absorbs water and hardens. As predicted by the theory of phase inversion dynamics [23], a highly porous matrix is formed within the injected depot. Drug residing in or near the pores is quickly released. This results in a system that releases a significant portion of the drug upon initial administration.

The Alzamer Depot technology uses solvents of low water miscibility that

Copyright © 2003 Marcel Dekker, Inc.

A



B

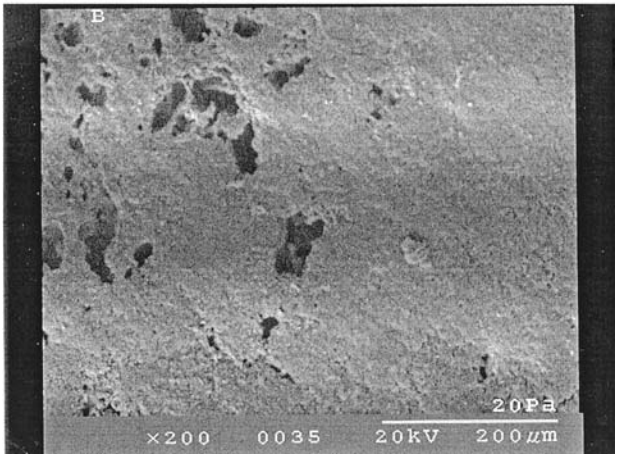


Figure 1 Gel structure after 4 days' implantation (PLGA RG502/solvent, 1:1, 10% loading). (A) NMP; (B) benzyl benzoate.

Copyright © 2003 Marcel Dekker, Inc.

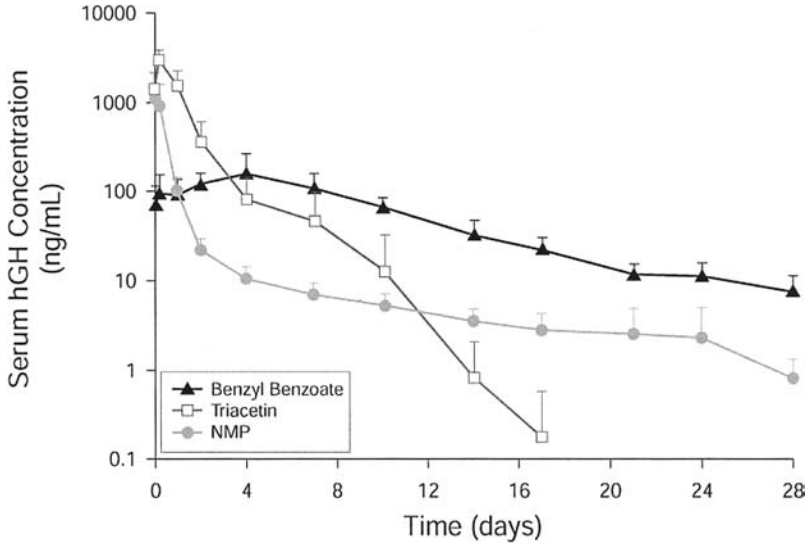


Figure 2 Effect of water solubility of solvent on hGH release in vivo (serum hGH levels in rats receiving a single depot injection).

slow the dynamics of phase inversion and alter the resultant morphology of the injected depot system. Figure 1B shows the morphology of a depot comprised of PLGA (L/G 50/50, $M_w \sim 16{,}000$) and benzyl benzoate (insoluble in water [25]). Slowing the phase inversion process significantly reduces the porosity of the system.

Figure 2 illustrates the effect of solvent choice and the phase-inversion process on drug release from Alzamer Depot technology. An initial drug burst is observed with the solvents triacetin and NMP; this initial burst is greatly reduced with the formulation containing benzyl benzoate as the solvent.

Choice of solvent also influences the time course of water absorption into the Alzamer Depot. Water absorption is substantially quicker for NMP and triacetin than for ethyl benzoate [20].

B. Protein Particle Development

Formulation of the protein particles dispersed in the Alzamer Depot can also affect the initial drug release. Densified particles can be produced by compressing protein and stearic acid (SA) together and redispersing the compacted protein into particles of defined size. Alternatively, the addition of divalent cations to lyophilized human growth hormone (hGH) is known to decrease solubility and dissolution [14]. Both techniques produce lower initial release from depot sys-

Copyright © 2003 Marcel Dekker, Inc.

tems than from lyophilized hGH alone dispersed in the Alzamer Depot gel [21]. Additionally, water absorption into the gel is slower with the densified hGH/SA particles than with the lyophilized hGH [21]. Initial release can thus be moderated and engineered to remain within a specified therapeutic window.

C. Drug Loading

The loading of drug in the gel can also affect the release kinetics. However, drug particle loading can be varied from 5% to 20% without inducing a significant initial drug burst and while maintaining sustained delivery.

D. Molecular Weight Decrease

Absorption of water into the depot initiates degradation of the PLGA copolymer. By week 2, the PLGA molecular weight has declined by approximately 30%; by week 3, the molecular weight has dropped by approximately 50%, with a greater decline for depots containing water-miscible solvents [21].

E. Choice of PLGA Polymer

The choice of PLGA polymer is a third critical factor that can affect the release of a drug from depot formulations. Changing the polymer molecular weight or the L/G ratio in the polymer can alter the interaction between the solvent and the polymer, resulting in alteration of the release profile.

III. PRECLINICAL EVALUATION

The PLGA polymer used in Alzamer Depot technology has an extensive history of use in sutures, clips, implants, and carriers for the sustained release of various pharmaceuticals [26]. The polymer is degraded by hydrolytic cleavage to form lactic and glycolic acids (i.e., parent monomers) that are normal metabolic compounds. The solvents and other excipients used in Alzamer Depot technology were initially screened for their performance characteristics and their safety/biocompatibility profile for parenteral use.

To date, more than 100 different Alzamer Depot formulations have been tested in rats. No remarkable adverse clinical observations or systemic signs of toxicity have been noted. Macroscopic evaluation of the subcutaneous injection sites has generally indicated mild irritation. Histopathological evaluation of the injection sites revealed typical responses to the presence of a foreign body in rats, with simple fibrosis or a mild to moderate granulomatous inflammation [24]. Biodegradation of the depot was observed to be partially complete after 56 days.

Copyright © 2003 Marcel Dekker, Inc.

To demonstrate the biological activity of the delivered drug, an Alzamer Depot containing hGH was administered to hypophysectomized rats; biological activity was confirmed by assessment of body weight gain and elevations in insulin-like growth factor-1 (IGF-1) levels for 28 days [24]. After preliminary studies in rats, the depot system should be evaluated in a second (nonrodent) species. The selection of the second species should be determined on a drug-by-drug basis and will often be determined by pharmacokinetic, pharmacodynamic, or immunological factors.

IV. IN VIVO/IN VITRO CORRELATION

While significant insight can be gained from in vitro testing of depot formulations containing water-miscible solvents, the testing of depot formulations containing water-immiscible solvents is far more difficult, and the results of these types of tests do not correlate with in vivo data in a straightforward fashion. Since it is extremely difficult to reproduce in vitro the complexity of the phenomena occurring in vivo, the performance of depot formulations must often be evaluated only in vivo. A reproducible drug release profile in vivo is achievable and has been confirmed in a large body of formulation work.

V. MANUFACTURING

Depot gels are manufactured using standard sizing and compounding equipment. For drugs that do not withstand terminal sterilization, aseptic manufacturing procedures are employed. As a product concept, Alzamer Depot technology is expected to be offered in convenient, prepackaged dosage forms with no premixing required.

VI. SUMMARY AND OUTLOOK

The Alzamer Depot technology platform was designed to provide sustained delivery of pharmaceutical agents for extended periods. Use of low-water-miscibility solvents in the platform controls the morphology of the injected depot via phase inversion, leading to a product with minimal initial drug burst. The release profile can be engineered by choice of depot solvent, polymer composition, formulation of the drug particle, and the loading of drug particles in the depot gel. Safety of the Alzamer Depot technology has been shown in preclinical work to date. While a useful in vitro release test that correlates with in vivo release has yet to be fully developed, a reproducible in vivo drug release profile is achievable and has been

Copyright © 2003 Marcel Dekker, Inc.

demonstrated in a large body of formulation work. Alzamer Depot technology represents a promising new platform technology for the sustained delivery of small molecules, proteins, and other biomolecules.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contributions of their colleagues on the Alzamer Depot team, especially in the nonclinical, analytical, and implant research-and-development departments, and the expert assistance of Susan Vintilla-Friedman in the editing and formatting of this chapter.

REFERENCES

1. DH Lewis. Controlled release of bioactive agents from lactide/glycolide polymers. In: M Chasin, R Langer, eds. Biodegradable Polymers as Drug Delivery Systems. New York: Marcel Dekker, 1990, pp. 1–41.
2. H Okada, H Toguchi. Biodegradable microspheres in drug delivery. Crit Rev Ther Drug Carrier Syst 12:1–99, 1995.
3. JL Cleland. Solvent evaporation processes for the production of controlled release biodegradable microsphere formulations for therapeutics and vaccines. Biotechnol Prog 14:102–107, 1998.
4. H Toguchi. Pharmaceutical manipulation of leuprorelin acetate to improve clinical performance. J Int Med Res 18(suppl 1):35–41, 1990.
5. WM Saltzman, MW Mak, MJ Mahoney, ET Duenas, JL Cleland. Intracranial delivery of recombinant nerve growth factor: release kinetics and protein distribution for three delivery systems. Pharm Res 16:232–240, 1999.
6. YY Hsu, T Hao, ML Hedley. Comparison of process parameters for microencapsulation of plasmid DNA in poly(D,L-lactic-co-glycolic) acid microspheres. J Drug Target 7:313–323, 1999.
7. KJ Lewis, WJ Irwin, S Akhtar. Development of a sustained-release biodegradable polymer delivery system for site-specific delivery of oligonucleotides: characterization of P(LA-GA) copolymer microspheres in vitro. J Drug Target 5:291–302, 1998.
8. B Bittner, M Morlock, H Koll, G Winter, T Kissel. Recombinant human erythropoietin (rhEPO) loaded poly(lactide-co-glycolide) microspheres: influence of the encapsulation technique and polymer purity on microsphere characteristics. Eur J Pharm Biopharm 45:295–305, 1998.
9. A Moore, P McGuirk, S Adams, WC Jones, JP McGee, DT O'Hagan, KH Mills. Immunization with a soluble recombinant HIV protein entrapped in biodegradable microparticles induces HIV-specific CD8+ cytotoxic T lymphocytes and CD4+ Th1 cells. Vaccine 13:1741–1749, 1995.
10. H Okada, Y Doken, Y Ogawa, H Toguchi. Preparation of three-month depot injectable microspheres of leuprorelin acetate using biodegradable polymers. Pharm Res 11:1143–1147, 1994.

Copyright © 2003 Marcel Dekker, Inc.

11. S Cohen, T Yoshioka, M Lucarelli, LH Hwang, R Langer. Controlled delivery systems for proteins based on poly(lactic/glycolic acid) microspheres. Pharm Res 8: 713–720, 1991.
12. L Garcia-Contreras, K Abu-Izza, DR Lu. Biodegradable cisplatin microspheres for direct brain injection: preparation and characterization. Pharm Dev Technol 2:53–65, 1997.
13. H Okada. One- and three-month release injectable microspheres of the LH-RH superagonist leuprorelin acetate. Adv Drug Del Rev 28:43–70, 1997.
14. JL Cleland, OL Johnson, S Putney, AJ Jones. Recombinant human growth hormone poly(lactic-co-glycolic acid) microsphere formulation development. Adv Drug Del Rev 28:71–84, 1997.
15. GL Yewey, EG Duysen, SM Cox, RL Dunn. Delivery of proteins from a controlled release injectable implant. Pharm Biotechnol 10:93–117, 1997.
16. HB Ravivarapu, KL Moyer, RL Dunn. Parameters affecting the efficacy of a sustained release polymeric implant of leuprolide. Int J Pharm 194: 181–191, 2000.
17. RA Jain, CT Rhodes, AM Railkar, AW Malick, NH Shah. Comparison of various injectable protein-loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices: in-situ-formed implant versus in-situ-formed microspheres versus isolated microspheres. Pharm Dev Technol 5:201–207, 2000.
18. RE Eliaz, J Kost. Characterization of a polymeric PLGA-injectable implant delivery system for the controlled release of proteins. J Biomed Mater Res 50:388–396, 2000.
19. PD Graham, KJ Brodbeck, AJ McHugh. Phase inversion dynamics of PLGA solutions related to drug delivery. J Control Rel 58:233–245, 1999.
20. KJ Brodbeck, JR DesNoyer, AJ McHugh. Phase inversion dynamics of PLGA solutions related to drug delivery. Part II. The role of solution thermodynamics and bathside mass transfer. J Control Rel 62:333–344, 1999.
21. KJ Brodbeck, S Pushpala, AJ McHugh. Sustained release of human growth hormone from PLGA solution depots. Pharm Res 16:1825–1829, 1999.
22. B Jeong, YH Bae, SW Kim. In situ gelation of PEG-PLGA-PEG triblock copolymer aqueous solutions and degradation thereof. J Biomed Mater Res 50:171–177, 2000.
23. BF Barton, JL Reeve, AJ McHugh. Observations on the dynamics of nonsolvent-induced phase inversion. J Polym Sci Polym Phys Ed 35:569–585, 1997.
24. R Bannister, K Baudouin, E Maze, N Modi, K Brodbeck. Biological activity, pharmacokinetics, and safety assessment of human growth hormone (hGH) delivered via a subcutaneous depot. Toxicol Sci 54:407, 2000.
25. The Merck Index. 12th ed. Whitehouse Station, NJ: Merck & Co., 1996, pp. 1162–1163.
26. Physicians' Desk Reference. Oradell, NJ: Medical Economics Company, 2000, pp. 581, 3094.

Copyright © 2003 Marcel Dekker, Inc.

54
The Atrigel Drug Delivery System

Richard L. Dunn
Atrix Laboratories, Fort Collins, Colorado, U.S.A.

I. INTRODUCTION

This chapter describes the development and unique features of the Atrigel® drug delivery system, and its application for the delivery of various drug products. The Atrigel system is a proprietary delivery system that can be used for both parenteral and site-specific drug delivery. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form a solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within the polymer matrix as it solidifies. The drug is then released over time as the polymer biodegrades. The technology for the Atrigel system is protected by 33 patents in the United States and 35 patents in the rest of the world. These patents cover the basic technology as well as process improvements.

The Atrigel system was initially developed by Dunn and co-workers at Southern Research Institute in Birmingham, Alabama in 1987 [1]. These investigators showed that the system formed an implant upon exposure to water and provided for sustained release of a number of drugs in vitro. Based upon these results, the technology was licensed to Vipont Research Laboratories (which later became Atrix Laboratories) for the subgingival delivery of antimicrobials to treat periodontal disease [2]. Its success in this application led to Atrix Laboratories purchasing the technology and all of its potential applications in 1991. Over the past 10 years, Atrix Laboratories has continued to develop the technology and to extend its use to a large number of both drug delivery and medical device applications.

Copyright © 2003 Marcel Dekker, Inc.

II. FORMULATION AND DEVELOPMENT

The rationale for developing the Atrigel technology was the need for a delivery system that had the simplicity and reliability of solid implant devices, but the convenience and ease of administration of microparticles. Solid implants that have reproducible release profiles can be made outside of the body using biodegradable polymers and well-controlled manufacturing processes such as extrusion, injection molding, and compression molding. However, because of their size, they require surgical implantation or the use of large trochars. Microparticles, on the other hand, can be injected into the body using standard needles and syringes. Unfortunately, the manufacturing processes for microparticles are often complex and difficult to control to give uniform batch-to-batch product [3]. The manufacturing process for the Atrigel system is not complicated in that the first step is the dissolution of the polymer into a biocompatible solvent. The drug is next added to the solution where it dissolves or forms a suspension. This drug/polymer mixture is then easily and conveniently injected into the body where it forms a solid implant inside the tissue. The ease of manufacture of the Atrigel system and its relatively pain-free subcutaneous injection into the body provide significant advantages over both solid implants and microparticles.

Most of the standard biodegradable polymers can be used in the Atrigel technology. These include the polyhydroxyacids, polyanhydrides, polyorthoesters, polyesteramides, and others. The polymers most often used are poly(DL-lactide), lactide/glycolide copolymers, and lactide/caprolactone copolymers because of their degradation characteristics and their approval by the Food and Drug Administration (FDA) [4,5]. The solvents employed in the Atrigel system to dissolve the polymers range from the more hydrophilic solvents such as dimethyl sulfoxide, *N*-methyl-2-pyrrolidone (NMP), tetraglycol, and glycol furol to the more hydrophobic solvents such as propylene carbonate, triacetin, ethyl acetate, and benzyl benzoate [6]. The most frequently used solvent is NMP because of its solvating ability and its safety/toxicology profile [7,8]. A Drug Master File on this solvent has been filed with the FDA.

The polymers are normally dissolved in the selected solvents to give formulations with polymer concentrations ranging from 10 to 80% by weight. The viscosity of the polymer solution depends upon the polymer concentration and the molecular weight of the polymer. The low-molecular-weight polymers at low polymer concentrations can be easily injected into the body using standard needles, and they can also be aerosolized for spray applications [9]. The high-molecular-weight polymers at high polymer concentrations may be used as gels or putties that can be placed into sites in the body where they solidify and provide support.

Using the lactide and lactide/glycolide copolymers dissolved in NMP, Atrix Laboratories has evaluated a number of product applications over the past

Copyright © 2003 Marcel Dekker, Inc.

10 years. Both in vitro and in vivo release studies were used to optimize the release characteristics of the formulations. For the in vitro studies, the drug is combined with the polymer solution and small drops of the mixture (about 50 mg) are added to phosphate-buffered saline solution. The receiving fluid is replaced at selected times with fresh solution, and the removed PBS solution is analyzed for drug concentration using a variety of analytical methods. Figure 1 shows the in vitro release of doxycycline hyclate from implants formed from three different polymers dissolved in NMP [2]. The more hydrophobic poly(DL-lactide-co-caprolactone) (PLC) gives the slowest release of the drug. The hydrophilic poly(DL-lactide-co-glycolide) (PLG) gives a low initial release of drug followed by a more rapid release once the polymer becomes hydrated. The poly(DL-lactide) (PLA) gives the highest initial burst of drug followed by a sustained release out to 8 days. Polymer molecular weight can also make a difference in the release of drug, as shown in Figure 2, for in vitro release of naltrexone base from an implant of an Atrigel formulation containing a 50/50 PLG copolymer in NMP [10]. The higher-molecular-weight polymer (IV = 0.73 dL/g) gives the highest burst and release of drug whereas the more moderate-molecular-weight polymer (IV = 0.35 dL/g) gives an almost zero-order release of drug.

The Atrigel system can be used to deliver both simple organic compounds and peptides and proteins. Shown in Figure 3 is the release of lidocaine hydrochloride in rats from implants of an Atrigel formulation using analysis of retrieved implants to determine cumulative percent release of drug and plasma analysis to verify the sustained release of the compound [11]. The data in both graphs repre-

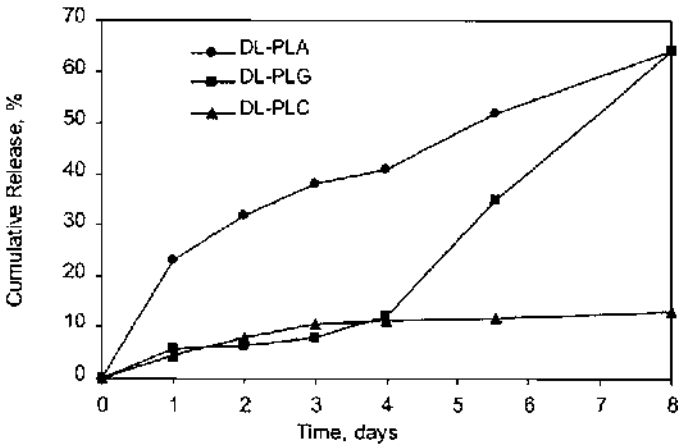


Figure 1 In vitro release of doxycycline hyclate from implants formed from Atrigel formulations with different polymer compositions.

Copyright © 2003 Marcel Dekker, Inc.

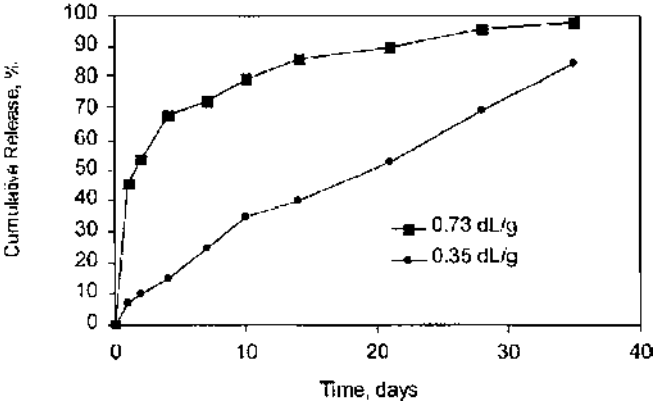


Figure 2 In vitro release of naltrexone from implants formed from Atrigel formulations prepared with 50/50 poly(DL-lactide-co-glycolide) polymers with different molecular weights.

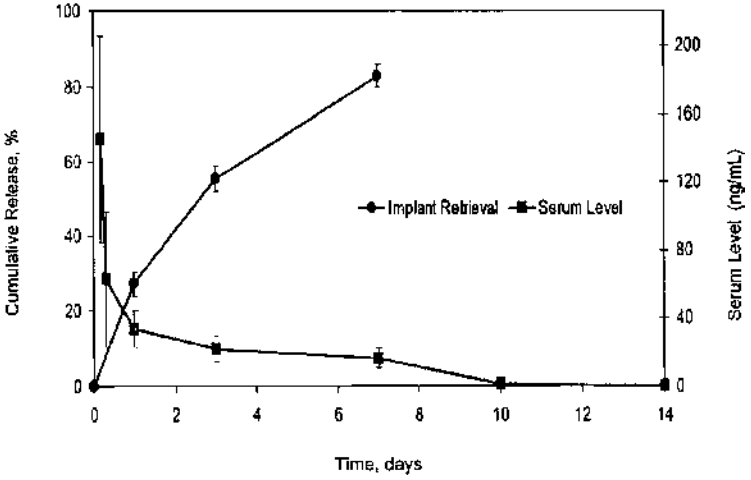


Figure 3 Release of lidocaine hydrochloride from intramuscular implants formed in rats with an Atrigel formulation.

Copyright © 2003 Marcel Dekker, Inc.

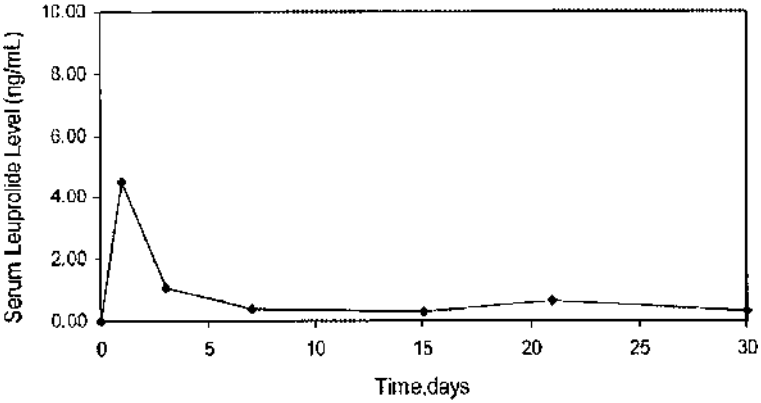


Figure 4 Serum concentrations of leuprolide acetate from subcutaneous implants in dogs with an Atrigel formulation.

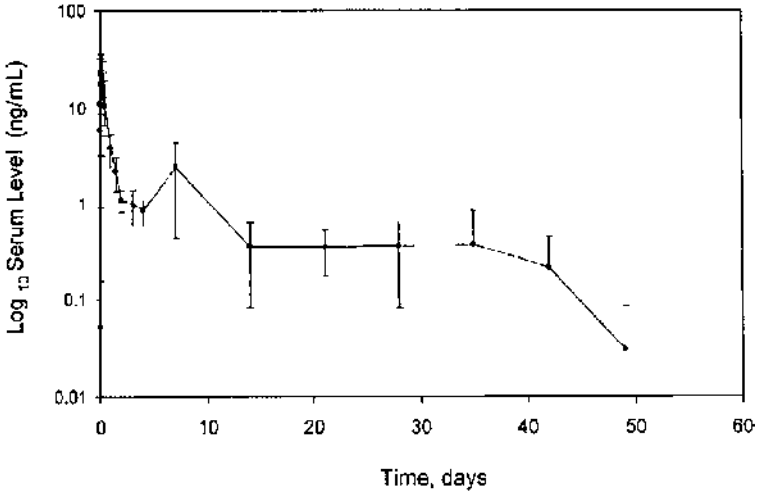


Figure 5 Serum concentrations of leuprolide acetate from subcutaneous implants in humans with an Atrigel formulation.

Copyright © 2003 Marcel Dekker, Inc.

sent the average of four studies and demonstrate the uniformity of drug release from different lots of formulation and different animal studies. Figure 4 gives the serum concentration of leuprolide acetate delivered in beagle dogs from implants formed from a 1-month Atrigel formulation [12]. After a small initial burst, the concentration of peptide is maintained over 30 days. A similar release profile was obtained from the same formulation when injected in humans, as shown in Figure 5.

III. MANUFACTURING, STERILIZATION, AND PACKAGING

Because the Atrigel system is a somewhat viscous polymer solution, it is not as easy to fill into vials and aspirate into syringes at the time of use as normal aqueous solutions. Therefore, the products currently marketed using this technology are filled into plastic syringes and packaged with foil-lined material to protect from moisture. Atrix Laboratories has developed custom-made equipment to fill a variety of plastic syringes with the polymer solutions within narrow fill volumes. Although an Atrigel polymer solution can be sterile-filtered, this is not the preferred method because of the viscosity of the solution. Therefore, gamma irradiation was evaluated and found to be a convenient method of terminal sterilization of the polymer solution. There is some loss in polymer molecular weight during gamma irradiation, but this is compensated for by using a polymer with a slightly higher molecular weight initially [13].

With the Atrigel system, the drug can often be dissolved within the polymer solution to form a uniphase product. In some cases, both the drug and polymer are stable as with the lidocaine hydrochloride product. However, because the drug and polymer are in solution, degradation of both components and reactions between the two may occur somewhat faster with some formulations than in a dry, solid state. With these products, the drug and polymer solution are maintained in separate syringes until immediately before use. At that time, the two syringes are coupled together and the contents mixed thoroughly by moving the materials back and forth between the two syringes. The homogeneous solution or mixture is drawn into one syringe, the two syringes are decoupled, and a needle is attached for injection. This type of product, A/B, provides for the maximum stability of the drug as well as the polymer. It also allows the drug to be sterilized by gamma irradiation in a dry state where it is often more stable.

Atrix Laboratories has developed specific syringe configurations that enable the two syringes to be connected directly together using luer lock fittings. In addition, these same luer lock fittings ensure that when the needle is attached to the syringe with the product, it remains in place during the injection. Atrix has also developed techniques for loading the drug into plastic syringes. One of these techniques is powder filling, and equipment that allows for precise control

Copyright © 2003 Marcel Dekker, Inc.

of fill weight has been custom-designed and fabricated. Currently, two marketed products utilize this technique. However, if the quantity of drug is too small to precisely powder-fill syringes or if the flow characteristics are not satisfactory, then the drug can be dissolved in water, sterile-filtered, and filled into plastic syringes where the drug can be lyophilized to a dry powder. This technique can also be used to provide a sterile product in cases where the drug is not stable to gamma irradiation. Atrix has developed proprietary methods to lyophilize drugs in plastic syringes that can be coupled with the polymer solution.

Using the techniques described above, the manufacturing of products with the Atrigel system can easily be scaled up to commercial quantities. First, the polymer is dissolved into the biocompatible solvent using a standard pharmaceutical product mixer. More recently, the polymer has been dissolved in the solvent by simply loading the two components into a sterile plastic container and placing it on a roll mixer. The polymer solution is then transferred from the plastic container to the syringe-filling equipment where it is loaded into individual syringes. The plastic container can then be discarded and the need for thorough cleaning is eliminated. The filled syringes are capped and placed into foil-lined packages to prevent moisture absorption. The drug is either powder-filled or lyophilized into syringes. If the drug is stable to gamma irradiation, then both the drug and polymer syringe are terminally sterilized by this method. If the drug is not stable to gamma irradiation, then the lyophilization is carried out under aseptic conditions to give a sterile drug syringe, and the polymer solution is sterilized by gamma irradiation. With this type of process, the manufacturing can easily accommodate the production of several hundred syringes to thousands in one batch.

IV. APPLICATIONS

Four products have already been approved by the FDA using the Atrigel technology. These are the Atridox® periodontal treatment product with subgingival delivery of doxycycline [14–16], the Atrisorb® GTR barrier product without any drug for guided tissue regeneration of peridontal tissue [17], the Atrisorb® D product with doxycycline for periodontal tissue regeneration [18], and the Doxyrobe® product with doxycycline for treatment of periodontal disease in companion animals. More recently, the Atrigel system has been utilized to develop 1-, 3-, and 4-month products (Eligard™) for the delivery of leuprolide acetate for treatment of prostate cancer [12,19–21]. These products have either started or completed phase III clinical studies. A 6-month product with leuprolide acetate is also in preclinical development. Based upon the clinical success of these products, it is anticipated that a number of additional applications of the technology will be possible. These include the delivery of small molecules, peptides, proteins, monoclonal antibodies, and vaccines. Some of these product applications will be

Copyright © 2003 Marcel Dekker, Inc.

in collaboration with major pharmaceutical companies, whereas others will be developed by Atrix Laboratories and licensed to larger companies after FDA approval. This has been the case with the periodontal products being licensed to CollaGenex and the leuprolide acetate products to Sanofi-Synthelabo.

V. CONCLUDING REMARKS

Although the current Atrigel technology appears to provide efficacious products with significant advantages over some other delivery systems, there have been, and continue to be, improvements made to the technology. These include methods to lower the initial drug burst, approaches to providing a more stable, ready-to-use formulation, and the use of new polymers and solvents to provide additional benefits in long-term drug release and tissue compatibility [22]. If successful, these modifications to the technology will increase the uniqueness of the Atrigel drug delivery system and its applicability to a wide variety of drug delivery products.

REFERENCES

1. RL Dunn, JP English, DR Cowsar, DP Vanderbilt. Biodegradable in situ forming implants and methods of producing the same. US patent 4,938,763, 1990.
2. RL Dunn, AJ Tipton, EM Menardi. A biodegradable in situ forming drug delivery system. Proc Int Symp Control Rel Bioact Mater 22:91–92, 1991.
3. M Radomsky, L Liu, Z Iwamoto. Synthetic polymers for nanosphere and microsphere products. In: J Senior, M Radomsky, eds. Sustained Release Injectable Products. Englewood, CO: Interpharm Press, 2000, pp. 181–202.
4. DH Lewis. Controlled release of bioactive agents from lactide/glycolide polymers. In: M Chasin, R Langer, eds. Biodegradable Polymers as Drug Delivery Systems. New York: Marcel Dekker, 1990, pp. 1–41.
5. CG Pitt. Poly-ε-caprolactone and its copolymers. In: M Chasin, R Langer, eds. Biodegradable Polymers as Drug Delivery Systems. New York: Marcel Dekker, 1990, pp. 71–120.
6. AJ Spiegel, MM Noseworthy. Use of non-aqueous solvents in parenteral products. J Pharm Sci 52:917–927, 1963.
7. KP Lee, C Chromey, R Culik. Toxicity of *N*-methyl-2-pyrrolidone (NMP): teratogenic, subchronic and two-year inhalation studies. Fundam Appl Toxicol 9:222–235, 1987.
8. B Akesson. Nordic experts group for criteria documentation for health risks to chemicals: *N*-methyl-2-pyrrolidone (NMP). Arbete och Halsa 40:1–24, 1994.
9. SM Fujita, JL Southard, GL Yewey, RL Dunn. Prevention of surgical adhesions using aerosoled biodegradable polymers. Trans Soc Biomater 17:384, 1994.

Copyright © 2003 Marcel Dekker, Inc.

10. AJ Tipton, WUV Trumpore, RL Dunn. A biodegradable, injectable delivery system for naltrexone. US-Japan Symposium on Drug Delivery, December 16–20, 1991.
11. EM Jarr, M Zhou, CM Balliu, JP Mitchell, DM Wilson, RL Dunn. Sustained release of lidocaine from an injectable implant system for treatment of post-operative pain. Proc Int Symp Control Rel Bioact Mater 26:631–632, 1999.
12. RL Dunn, B Chandrashekar, D Anna, S Garrett, L Southard. An in-situ forming delivery system for peptides and proteins. US-Japan Symposium on Drug Delivery, December 14–19, 1997.
13. BK Lowe, RL Norton, EL Keeler, KR Frank, AJ Tipton. The effects of gamma irradiation on poly(DL-lactide) as a solid and in *N*-methyl-2-pyrrolidone solutions. Trans Soc Biomater 16:54, 1993.
14. AM Polson, RL Dunn, JC Fulfs, KC Godowski, AP Polson, GL Southard, GL Yewey. Periodontal pocket treatment with subgingival doxycycline from a biodegradable system. J Dent Res 72:360, 1993.
15. A Polson, S Garrett, N Stoller, C Bandt, P Haner, W Killoy, G Southard, S Duke, G Bogle, C Drisko, L Friesen. Multicenter comparative evaluation of subgingivally delivered sanguinarine and doxycycline in the treatment of periodontitis. II. Clinical results. J Periodontol 68:119–126, 1997.
16. S Garrett. Local delivery of doxycycline for the treatment of periodontitis. Compendium 20:437–448, 1999.
17. AM Polson, G Southard, R Dunn, AP Polson, J Billen, L Laster. Initial study of guided tissue regeneration in class III furcation results after use of a biodegradable barrier. Int J Periodont Rest Dent 15:45–55, 1995.
18. JS Garrett, KM Holland, BA Coonts, LA Moore, KE Cady, C Yarborough, R Bawa, RL Dunn. An in situ forming guided tissue regeneration barrier with doxycycline. Trans Soc Biomater 22:251, 1999.
19. HB Ravivarapu, KL Moyer, RL Dunn. Parameters affecting the efficacy of a sustained release polymeric implant of leuprolide. Int J Pharm 194:181–191, 2000.
20. HB Ravivarapu, KL Moyer, RL Dunn. Sustained suppression of pituitary-gonadal axis with an injectable, in-situ forming implant of leuprolide acetate. J Pharm Sci 89:732–741, 2000.
21. HB Ravivarapu, KL Moyer, RL Dunn. Sustained activity and release of leuprolide acetate from an in-situ forming polymeric implant. Pharm Sci Tech 2000.
22. M Zhou, C Balliu, K Tow, R Dunn. Preparation and evaluation of an Atrigel controlled release formulation for intratumoral delivery of floxuridine. Pharm Sci 1(suppl):S-582, 1998.

Copyright © 2003 Marcel Dekker, Inc.

55

Long-Term Controlled Delivery of Therapeutic Agents via an Implantable Osmotically Driven System: The DUROS Implant

Jeremy C. Wright,* Anne E. Chester, Roman J. Skowronski,† and Catherine Lucas
ALZA Corporation, Mountain View, California, U.S.A.

I. INTRODUCTION

The DUROS® implant is a sterile, nonerodible, drug-dedicated, osmotically driven system developed by ALZA Corporation to provide long-term, controlled drug delivery. It was initially developed as a delivery platform for therapeutic agents that must be administered parenterally to avoid degradation following oral administration, including peptides, proteins, and other complex biologically active molecules. The first application of DUROS technology—Viadur® (leuprolide acetate implant)—provides zero-order delivery of leuprolide, a synthetic nonapeptide gonadotropin-releasing hormone (GnRH) agonist. DUROS technology is also well suited for delivery of other potent biomolecules that require long-term, controlled, parenteral administration, including those that require steady-state serum concentrations and those that have a narrow therapeutic window or a short half-life. Moreover, while Viadur provides zero-order delivery, DUROS technology can be adapted to produce other patterns of drug delivery [1].

---

* *Current affiliation*: DURECT Corporation, Cupertino, California, U.S.A.
† *Current affiliation*: Alexza Molecular Delivery Corporation, Palo Alto, California, U.S.A.
DUROS is a registered trademark of ALZA Corporation.

Copyright © 2003 Marcel Dekker, Inc.

Alternative methods for delivery of biomolecules include immediate-release injections (intramuscular, subcutaneous, and intravenous bolus), microsphere and other depot injections, inhalation, and infusion via pumps. Several of these methods require routine patient cooperation and consequently can present compliance problems. Furthermore, immediate-release injections and inhaled formulations generally produce a high initial blood concentration followed by a rapid decline [2–4]. Microsphere and other depot injections can release significant amounts of drug in an initial burst—up to 20–50% of the dose with some systems [5–7]. In addition, if a patient experiences an adverse reaction to a depot injection, the drug cannot be immediately discontinued. External infusion pumps can be cumbersome: percutaneous access must be established and maintained, and there is the concomitant risk of infection. Although more convenient, implanted electromechanical infusion pumps have, to date, been fairly large and expensive, and they are available for a limited number of applications. In addition, delivery of biomolecules is complicated by the difficulty of developing formulations that remain stable at body temperature for extended periods.

The DUROS implant offers an alternative to these other methods of biomolecule delivery. It provides long-term, controlled delivery without the need for patient intervention. In addition, it is small, is inserted subcutaneously during an office procedure, and can be removed to discontinue therapy immediately. Furthermore, continuous administration via the DUROS system offers the potential for dose-sparing reductions in overall drug usage.

The DUROS system [8] evolved from ALZA's work with other implantable osmotic systems: the ALZET® osmotic pump* (a miniaturized system that provides zero-order delivery of biologically active molecules and has been extensively used in animal studies by researchers throughout the world [9]), and research on drug-dedicated osmotic systems for veterinary applications [10,11].

II. DUROS PRODUCTS

The first DUROS product to receive regulatory approval was Viadur (leuprolide acetate implant)† (Fig. 1), which delivers leuprolide, a synthetic nonapeptide, at a continuous rate for a 1-year period (Fig. 2). Viadur is approved by the U.S. Food and Drug Administration for palliative treatment of advanced prostate cancer. The release properties of a number of other biomolecules—including human growth hormone (hGH), α-interferon, glucagon-like peptide 1 (GLP-1), and

* Now marketed by the DURECT Corporation, Cupertino, CA.

† U.S. marketing rights: Bayer Corporation, Pharmaceutical Division, West Haven, CT.

Copyright © 2003 Marcel Dekker, Inc.

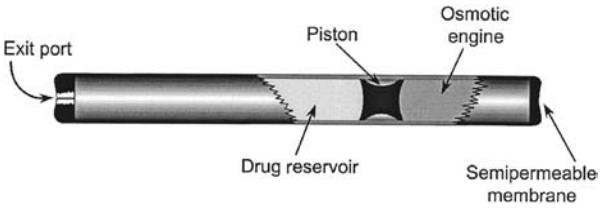


Figure 1 Cutaway view of a DUROS implant showing the titanium alloy outer cylinder, osmotic engine, piston, and drug reservoir; the implant is capped at one end with a semipermeable membrane and at the other end with the exit port. (From Ref. [24], JC Wright, CL Stevenson, GR Stewart. Pumps/Osmotic–DUROS® Osmotic Implant for Humans. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. Copyright © 1999, John Wiley and Sons, Inc. Reprinted by permission of John Wiley and Sons, Inc.)

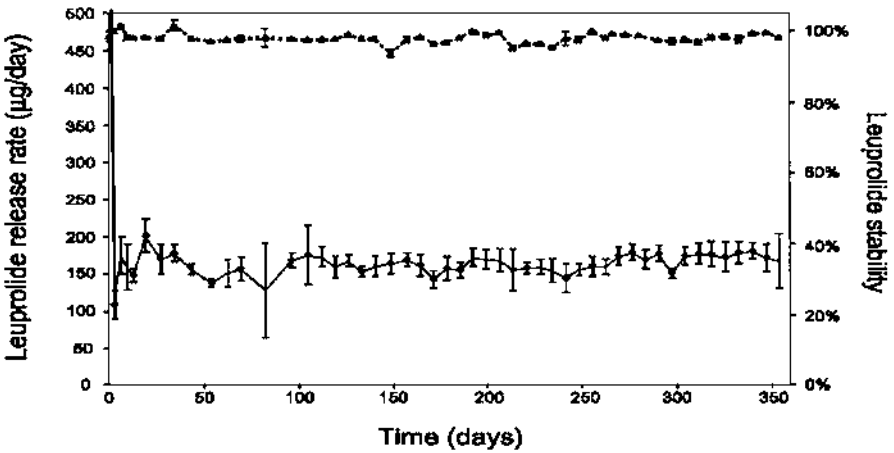


Figure 2 In vitro delivery and stability of leuprolide (mean ± standard deviation) from DUROS implants ($n = 6$) into phosphate-buffered saline maintained at 37°C; system output was measured by reverse-phase high-pressure liquid chromatography; drug formulation of leuprolide dissolved in DMSO. (From Ref. [24], JC Wright, CL Stevenson, GR Stewart. Pumps/Osmotic–DUROS® Osmotic Implant for Humans. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. Copyright © 1999, John Wiley and Sons, Inc. Reprinted by permission of John Wiley and Sons, Inc.)

Copyright © 2003 Marcel Dekker, Inc.

salmon calcitonin—were evaluated as part of the DUROS research program to ensure flexibility in the system's basic design [1,12,13].

III. SYSTEM DESIGN AND OPERATING PRINCIPLES

The DUROS implant consists of an outer cylinder that is capped at one end by a semipermeable membrane and at the other end by an exit port (Fig. 1). Within the cylinder are an osmotic engine, a piston, and the drug formulation. In Viadur (leuprolide acetate implant), the drug formulation is leuprolide acetate dissolved in dimethyl sulfoxide (DMSO), a nonaqueous, polar, aprotic solvent [14]. This peptide formulation remains stable for 1 year at body temperature (Fig. 2) [15].

Drug delivery from the DUROS system is controlled by osmotic principles. The membrane at the end of the implant is permeable to water but impermeable to the osmotic solutes in the osmotic engine. Therefore, water moves through the membrane in response to the osmotic gradient between the osmotic engine [typically saturated sodium chloride (NaCl)] and the extracellular fluid in the subcutaneous space. The osmotic engine then swells, displacing the piston and thereby decreasing the volume of the compartment that contains the drug formulation. This results in delivery of the drug through the exit port at a precisely controlled rate.

The rate of drug release from the DUROS system (dm/dt) is described by Eq. (1):

$$\mathrm{dm/dt} = (A/h)k\Delta\pi c \tag{1}$$

In Eq. (1), A is the cross-sectional area of the membrane available for water transport, h is the membrane thickness, k is the effective permeability of the membrane, $\Delta\pi$ is the osmotic pressure difference across the membrane, and c is the concentration of the drug formulation.

By manipulating variables in the above equation (A, h, k, $\Delta\pi$, and c), a variety of delivery patterns can be obtained [16]. By keeping the variables constant, DUROS systems can be engineered to provide extended zero-order delivery. Zero-order delivery of leuprolide for 1 year from a DUROS implant is shown in Figure 2. Zero-order delivery has also been demonstrated for hGH for 3 months and for GLP-1 for 3 months [12,13].

Suspensions and solutions used in DUROS implants can be formulated at up to 50% total drug loading. To date, two DUROS systems have been developed: a 150-μL capacity system with outer dimensions of 4 by 45 mm, and a 500-μL capacity system with outer dimensions of 6 by 46 mm. Viadur, which uses the 4-by-45-mm system, contains leuprolide acetate equivalent to 65 mg leuprolide free base. With the larger system (500 μL), the maximum drug-loading capacity is 250 mg. If a higher drug load capacity is needed, larger system sizes could

Copyright © 2003 Marcel Dekker, Inc.

be developed, depending on the specific therapeutic application and patient population.

IV. PRECLINICAL DEVELOPMENT OF DUROS AND VIADUR

The performance characteristics and safety profile of materials in the DUROS implant have been screened with reference to International Conference on Harmonisation (ICH) guidelines. The testing program included cell-based assays, rodent-model studies, and nonrodent-model studies. Circulating concentrations of drug were monitored in rodent and nonrodent species; drug delivery was quantified by measuring the amount of drug that remained in the implant when it was removed from the body.

Materials in Viadur (leuprolide acetate implant) were screened for safety at several stages: as raw materials, fabricated components, and the completed implant. Initial materials selection included a literature review for information on biocompatibility. Viadur materials were also screened by cytotoxicity tests, genotoxicity tests, and U.S. Pharmacopeia Class VI tests for plastic materials [17,18]. Viadur has been evaluated in swine, rats, and dogs for periods of 2 weeks–1 year and was found to be well tolerated, with mild encapsulation and mild-to-moderate local tissue reactions.

The nonclinical program required for regulatory submission of a DUROS system may typically include the following:

Local tolerance studies, in vivo performance studies, and pharmacokinetics studies.
ISO 10993 biocompatibility studies.
Subchronic toxicity and irritation studies.
Genotoxicity studies.
Characterization and quantitation of degradation products, impurities, and leachates from the drug substance, drug product, other system components, and the manufacturing process.
Chronic toxicity and irritation study in rodents and nonrodent species to evaluate long-term systemic and local effects.
Other studies determined on a drug-by-drug basis (e.g., absorption/distribution/metabolism/excretion studies, pharmacodynamics studies).

V. CLINICAL DEVELOPMENT OF VIADUR

Viadur delivers leuprolide for the palliative treatment of advanced prostate cancer. Leuprolide, a GnRH agonist, acts on the pituitary-testicular axis to produce

Copyright © 2003 Marcel Dekker, Inc.

an initial, transient increase in circulating testosterone, followed by profound long-term suppression to castrate concentrations. Suppression of circulating testosterone by various means has long been the primary therapeutic approach to the management of advanced prostate cancer [19,20].

In two open-label, noncomparative, multicenter studies, 131 patients with prostate cancer were treated with Viadur for up to 2 years. The implant was inserted subcutaneously in the inner aspect of the upper arm using a custom-designed implanter. A dose-ranging study assessed 51 patients treated with one ($n = 27$) or two ($n = 24$) implants for 12 months [21]. Because both one and two implants effectively suppressed testosterone in the first year of the dose-ranging study, the confirmatory study evaluated 80 patients treated with one implant for 12 months [22]. In each study, the implants were removed at the end of the first 12 months, and patients were offered the opportunity to continue in a 12-month study extension; if they chose to continue, one new implant was inserted. Of the 122 patients completing the first year, 118 (97%) chose to participate in the second year.

With Viadur, steady-state serum leuprolide concentrations were achieved (Fig. 3), and serum leuprolide concentrations were proportional to the number

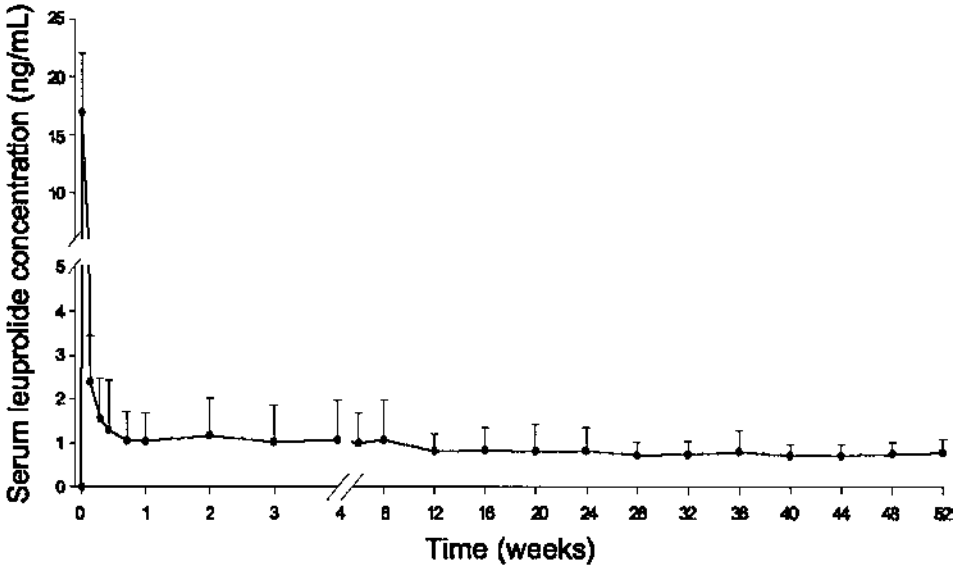


Figure 3 Serum leuprolide concentrations (mean ± standard deviation) from the first year of the confirmatory clinical study ($n = 80$), measured by solid-phase extraction liquid chromatography–tandem mass spectrometry.

Copyright © 2003 Marcel Dekker, Inc.

of implants. In patients with one implant, the mean serum leuprolide concentration was 16.9 ng/mL at 4 h after implant insertion and 2.4 ng/mL at 24 h. Thereafter, leuprolide was released at a constant rate. Mean serum leuprolide concentrations were maintained at approximately 0.9 ng/mL (range, 0.3–3.1 ng/mL) for 12 months.

In both clinical studies, testosterone exhibited the classic response seen after administration of a GnRH agonist—an initial increase followed by profound suppression. Once serum testosterone was continuously suppressed, it remained below the castrate threshold (<50 ng/dL) in all patients for the remainder of the initial 12-month study periods and the 12-month study extensions (Fig. 4). In addition, the serum prostate-specific antigen (PSA) concentration—an indication of prostate cell activity and objective treatment response—decreased in all patients after they began treatment.

Physicians participating in the clinical studies expressed satisfaction with the implant insertion, removal, and reinsertion procedures, with more than 80% of the procedures described as "somewhat easy" or "very easy." Most patients found the implant to be comfortable and convenient. The majority of local reac-

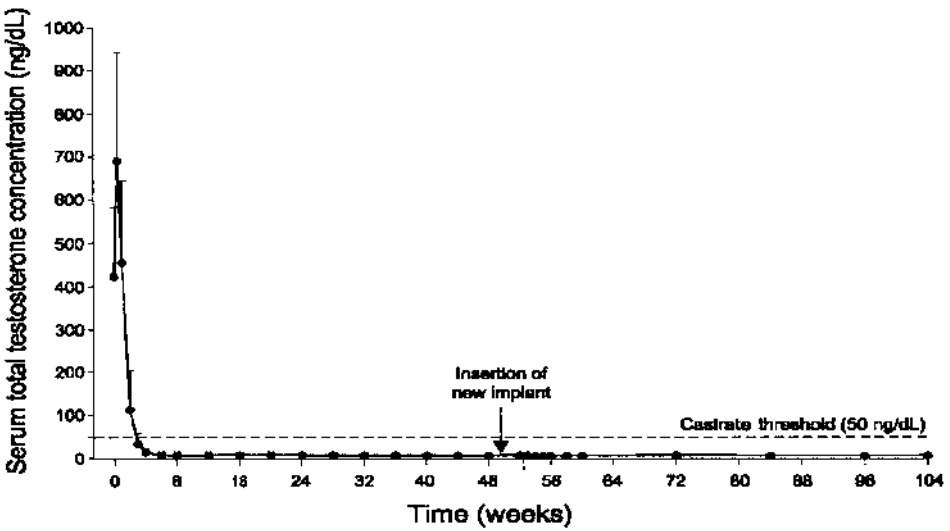


Figure 4 Serum total testosterone concentrations (mean ± standard deviation) in prostate cancer patients who received one implant for both 12-month periods in the dose-ranging and confirmatory clinical studies ($n = 107$), measured by extraction column chromatography followed by radioimmunoassay.

Copyright © 2003 Marcel Dekker, Inc.

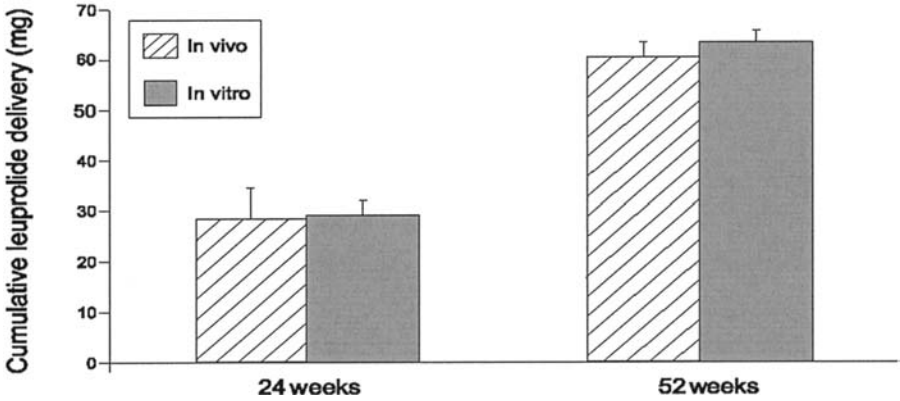


Figure 5 In vivo/in vitro correlation of leuprolide delivery (mean ± standard deviation) from DUROS implants 24 weeks after implantation ($n = 3$ in vivo in rats, $n = 5$ in vitro) and 52 weeks after implantation ($n = 6$ in vivo in dogs, $n = 9$ in vitro).

tions associated with implant insertion or removal began and resolved within the first 2 weeks.

VI. IN VIVO/IN VITRO CORRELATION

Osmotic systems exhibit good correlation between in vitro and in vivo delivery rates [11,23]. Figure 5 illustrates the in vivo/in vitro correlation for leuprolide delivery from a DUROS® implant 24 and 52 weeks after implant insertion in rodents and dogs [24]. Correlation to within ±10% was also observed for leuprolide delivery from DUROS implants in humans [25]. The stability of leuprolide in the DUROS implant was also comparable in the in vivo and in vitro conditions [25].

VII. MATERIALS AND MANUFACTURING

A. Materials

The outer cylinder of the DUROS implant can be manufactured from a number of materials. The titanium alloy used in Viadur was chosen because of its biocompatibility [26], compatibility with the drug formulation, strength, and ease of fabrication. Composition of the semipermeable membrane that caps one end of the cylinder is controlled to ensure both the proper water permeation rate and

Copyright © 2003 Marcel Dekker, Inc.

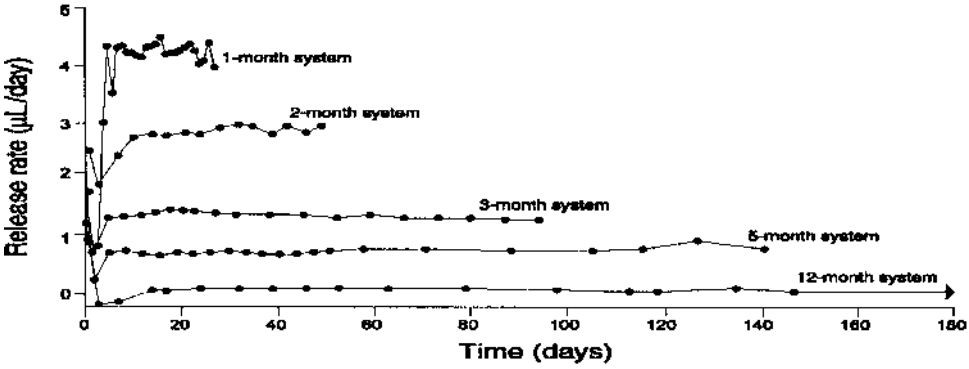


Figure 6 Mean in vitro volumetric delivery rates at 37°C from DUROS implants designed to deliver an agent for 1, 2, 3, 5, or 12 months ($n = 10$ per delivery duration); implants were filled with aqueous blue dye that was released into phosphate-buffered saline. (From Ref. [24], JC Wright, CL Stevenson, GR Stewart. Pumps/Osmotic–DUROS® Osmotic Implant for Humans. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. Copyright © 1999, John Wiley and Sons, Inc. Reprinted by permission of John Wiley and Sons, Inc.)

impermeability to ions and other components of the osmotic engine. The membrane can be engineered to provide a range of delivery durations (Fig. 6), from less than 1 month to more than 1 year. Semipermeable polymers that are suitable for fabrication of the membrane include cellulose esters, polyurethanes, and polyamides [8]. The semipermeable membrane of Viadur is made of polyurethane. The exit port that caps the other end of the cylinder has a channel that is sufficiently long and narrow to minimize diffusional or uncontrolled convective contributions to drug flux, and also to minimize back-diffusion of water and other components of the extracellular fluid into the drug reservoir.

The DUROS osmotic engine usually contains NaCl formulated as a tablet, with the necessary tableting excipients. It contains sufficient NaCl to remain saturated throughout its expansion, as it absorbs water from the extracellular space. The piston that separates the osmotic engine from the drug formulation is constructed from an elastomeric material that is suitable for drug contact and implantable use. To achieve shelf life and delivery duration requirements, the piston material must not creep or compression set substantially.

Development of protein formulations that are stable for extended durations at body temperature is extremely challenging. Because most proteins are subject to hydrolysis in aqueous solution, nonaqueous solutions and suspensions of proteins have been produced during the DUROS development program [27,28]. These nonaqueous formulations stabilize the proteins for extended periods. The

Copyright © 2003 Marcel Dekker, Inc.

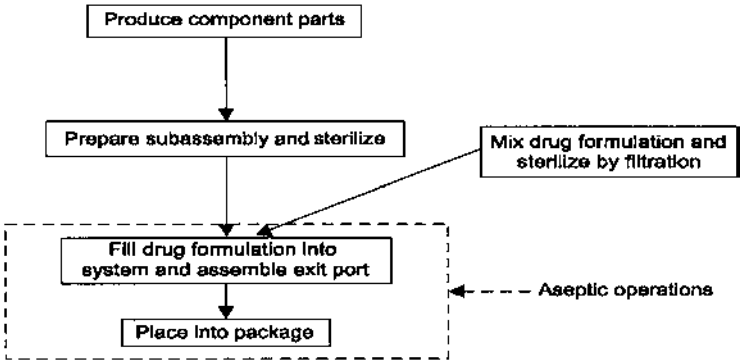

Produce component parts
Prepare subassembly and sterilize
Mix drug formulation and sterilize by filtration
Fill drug formulation into system and assemble exit port
Aseptic operations
Place into package

Figure 7 Manufacturing flow diagram for Viadur (leuprolide acetate implant).

DUROS system protects the formulation from extracellular fluids until it is delivered. In development of Viadur, leuprolide was found to be highly soluble in DMSO, and concentrated solutions of leuprolide in DMSO exhibited excellent stability at 37°C for more than 1 year [14,15]. In addition, as part of the broader DUROS development program, suspension formulations of α-interferon, factor IX, GLP-1, and hGH have been stabilized for periods of 3 months–1 year [1,12,13,29].

B. Manufacturing Overview

Aseptic manufacturing processes for Viadur have been developed and validated (Fig. 7). Individual components are manufactured, and then a subassembly consisting of the reservoir, membrane, osmotic engine, and piston is fabricated. This subassembly is sterilized by irradiation. In aseptic operations, the drug formulation is added to the subassembly, and the exit port is installed. Packaging and labeling complete the manufacturing process.

VIII. REGULATORY ASPECTS

Although the DUROS implant has device-like characteristics, the outcome of treatment with a DUROS system is achieved through the pharmacological action of the drug. Accordingly, DUROS products are regulated as drugs in the United States, and regulatory review is through the appropriate drug review division of the Food and Drug Administration.

Drugs that have completed clinical studies with a different dosage form

Copyright © 2003 Marcel Dekker, Inc.

and those that have received regulatory approval before incorporation in a DUROS delivery system may be able to utilize a novel regulatory approach to product registration. For example, when safety and efficacy data have been generated with a different dosage form of a drug, those data, together with pharmacokinetic data from the DUROS delivery system, may support a more limited safety and efficacy development program conducted with the DUROS product.

IX. OUTLOOK

The DUROS implant can be adapted to deliver a variety of potent therapeutic molecules at controlled rates. The development of protein solutions and suspensions that remain stable for prolonged periods at body temperature makes the DUROS system particularly well suited for prolonged parenteral delivery of peptides, proteins, and other complex biomolecules. Additionally, the properties of the system make it potentially useful for drugs that should be delivered at a precisely controlled rate, those that have enhanced safety or efficacy when stable circulating concentrations are maintained, those with a narrow therapeutic window, and those with a short half-life. Potential applications of DUROS technology include delivery of nucleic acids for gene therapy, site-directed delivery via catheters, and pulsatile or patterned delivery. Furthermore, additional miniaturization could lead to multidrug delivery configurations and on-demand delivery of small dosages.

X. SUMMARY

The DUROS implant provides long-term, controlled delivery of a range of biologically active molecules. A key element of the initial application of DUROS technology has been the development of nonaqueous formulations of biomolecules that remain stable at body temperature for extended periods. Viadur, the first DUROS product to obtain U.S. regulatory approval, maintains steady-state serum leuprolide concentrations, produces the desired pharmacodynamic effects, was well tolerated in clinical studies, and provides a means of long-term drug delivery that was favorably received by investigators and patients. As DUROS technology is more broadly applied, it will enable the therapeutic benefits of many potent biomolecules to be more fully realized.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contributions of their colleagues on the Viadur project team and the DUROS implant research-and-development team and the editorial assistance of Sharon Irving.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. CL Stevenson, F Theeuwes, JC Wright. Osmotic implantable delivery systems. In: DL Wise, ed. Handbook of Pharmaceutical Controlled Release Delivery. New York: Marcel Dekker, 2000, pp. 225–254.
2. JS Patton. Pulmonary delivery of drugs for bone disorders. Adv Drug Del Rev 42: 239–248, 2000.
3. JS Patton, J Bukar, S Nagarajan. Inhaled insulin. Adv Drug Del Rev 35:235–247, 1999.
4. A Adjei, J Garren. Pulmonary delivery of peptide drugs: effect of particle size on bioavailability of leuprolide acetate in healthy volunteers. Pharm Res 7:565–569, 1990.
5. Physician's Desk Reference. Nutropin Depot (somatropin [rDNA origin] for injectable suspension). Montvale, NJ: Medical Economics Company, 2000.
6. JL Cleland, A Mac, B Boyd, J Yang, ET Duenas, D Yeung, D Brooks, C Hsu, H Chu, V Mukku, AJ Jones. The stability of recombinant human growth hormone in poly (lactic-co-glycolic acid) (PLGA) microspheres. Pharm Res 14:420–425, 1997.
7. Y Ogawa, H Okada, T Heya, T Shimamoto. Controlled release of LHRH agonist, leuprolide acetate, from microcapsules: serum drug level profiles and pharmacological effects in animals. J Pharm Pharmacol 41:439–444, 1989.
8. JR Peery, KE Dionne, JB Eckenhoff, FA Landrau, SD Lautenbach, JA Magruder, JC Wright. Sustained delivery of leuprolide using an implantable system. US patent 5,728,396, 1998.
9. L Perkins, C Peer, V Fleming. Pumps/osmotic—ALZET® system. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. Vol 2. New York: John Wiley & Sons, 1999, pp. 900–906.
10. J Magruder. Pumps/osmotic: VITS veterinary implant. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. Vol 2. New York: John Wiley & Sons, 1999, pp. 906–909.
11. JR Zingerman, JR Cardinal, RT Chern, J Holste, JB Williams, B Eckenhoff, J Wright. The in vitro and in vivo performance of an osmotically controlled delivery system—IVOMEC SR bolus. J Control Rel 47:1–11, 1997.
12. C Stevenson, P Fereira, M Tan, R Ayer, H Dehnad, S Berry. Glucagon like peptide suspension stability and delivery from a DUROS® implant. Proc Int Symp Control Rel Bioact Mater 27:986–987, 2000.
13. H Dehnad, S Berry, P Fereira, R Ayer, A O'Brien, G Chen, D Priebe, J Matsuura, A Muchnik, LL Kang, A Chester, JC Wright. Functionality of osmotically driven, implantable therapeutic systems (DUROS® implants): effect of osmotic pressure and delivery of suspension formulations of peptides and proteins. Proc Int Symp Control Rel Bioact Mater 27:1016–1017, 2000.
14. CL Stevenson, SJ Prestrelski. Non-aqueous polar aprotic peptide formulations. US patent 5,932,547, 1999.
15. J Wright, G Chen, M Cukierski, C Davis, C Falender, D Mabanglo, J Peery, L Ponnekanti, R Skowronski, C Stevenson, S Tao, J Brown. DUROS™ leuprolide im-

Copyright © 2003 Marcel Dekker, Inc.

plant for continuous one-year treatment of prostate cancer. Proc Int Symp Control Rel Bioact Mater 25:516–517, 1998.
16. JC Wright, CL Stevenson. Pumps/osmotic—introduction. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. Vol 2. New York: John Wiley & Sons, 1999, pp. 896–900.
17. United States Pharmacopeia 23. Rockville, MD: The United States Pharmacopeial Convention, 1995, pp. 1699–1703.
18. United States Pharmacopeia 24. Rockville MD: The United States Pharmacopeial Convention, 2000, pp. 1832–1836.
19. ED Crawford, EP DeAntonio, F Labrie, FH Schroder, J Geller. Endocrine therapy of prostate cancer: optimal form and appropriate timing. J Clin Endocrinol Metab 80:1062–1078, 1995.
20. C Huggins, CV Hodges. Studies of prostate cancer. I. Effect of castration, estrogen, and androgen injections on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1:293–297, 1941.
21. JE Fowler, JE Gottesman, CF Reid, GL Andriole, MS Soloway. Safety and efficacy of an implantable leuprolide delivery system in patients with advanced prostate cancer. J Urol 164:730–734, 2000.
22. JE Fowler, M Flanagan, DM Gleason, IW Klimberg, JE Gottesman, R Sharifi. Evaluation of an implant that delivers leuprolide for 1 year for the palliative treatment of prostate cancer. Urology 55:639–642, 2000.
23. B Eckenhoff, F Theeuwes, F Urquhart. Osmotically actuated dosage forms for rate-controlled drug delivery. Pharm Tech 11:96–105, 1987.
24. JC Wright, CL Stevenson, GR Stewart. Pumps/osmotic—DUROS® osmotic implant for humans. In: E Mathiowitz, ed. Encyclopedia of Controlled Drug Delivery. Vol. 2. New York: John Wiley & Sons, 1999, pp. 909–915.
25. JC Wright, ST Leonard, CL Stevenson, JC Beck, G Chen, RM Jao, PA Johnson, J Leonard, RJ Skowronski. An in vivo/in vitro comparison with a leuprolide osmotic implant for the treatment of prostate cancer. J Control Rel 75:1–10, 2001.
26. RJ Solar. Corrosion resistance of titanium surgical implant alloys: a reveiw. In: BC Syrett, A Acharya, eds. Corrosion and Degradation of Implant Materials. ASTM STP 684. Easton, MD: American Society for Testing and Materials, 1979, pp. 259–273.
27. JB Eckenhoff, LL Holladay, JJ Leonard, IKM Leung, SA Tao, JA Magruder, J Carr, J Wright. Peptide/protein suspending formulations. US patent 5,904,935, 1999.
28. CL Stevenson, SA Tao, SJ Prestrelski, JB Eckenhoff, JC Wright, JJ Leonard. Nonaqueous protic peptide formulations. US patent 5,981,489, 1999.
29. VM Knepp, A Muchnik, S Oldmark, L Kalashnikova. Stability of nonaqueous suspension formulations of plasma derived factor IX and recombinant human alpha interferon at elevated temperatures. Pharm Res 15:1090–1095, 1998.

Copyright © 2003 Marcel Dekker, Inc.

56

Long-Acting Protein Formulations—ProLease Technology

OluFunmi L. Johnson and Paul Herbert
Alkermes Incorporated, Cambridge, Massachusetts, U.S.A.

I. INTRODUCTION

Therapeutic proteins are administered frequently by the parenteral route because of their low oral bioavailability and short in vivo half-lives. Several peptides and small-molecule drugs have been successfully encapsulated in injectable biodegradable matrices to provide long-acting sustained release of the encapsulated drug [1,2]. These formulations offer the potential to improve patient compliance, efficacy of the drug, expansion of therapeutic indications, and a reduction in undesirable side effects. However, development of similar formulations of macromolecules such as proteins has been a significant challenge because of the difficulty of maintaining the protein in its native and biologically active form through the encapsulation process. The processes used to encapsulate small molecules and peptides typically involve the formation of emulsions and the generation of an oil-water interface. The amphipathic nature of proteins causes them to accumulate at the interface; potentially disrupting their three-dimensional structure and resulting in loss of biological activity. Additionally, the protein is usually encapsulated as an aqueous solution and protein degradation may occur via water-mediated pathways such as aggregation, deamidation, hydrolysis, and oxidation.

Copyright © 2003 Marcel Dekker, Inc.

II. PROLEASE DELIVERY SYSTEM

The ProLease delivery system was designed specifically to encapsulate fragile biomolecules and overcome the problems associated with emulsion encapsulation processes [3]. It is critical that the integrity and stability of the protein is maintained through the encapsulation process and the encapsulation technology should provide the means to generate a broad range of in vivo release profiles to match the intended application. The encapsulation technology should be scalable and enable the production of sterile product at a commercially viable scale under cGMP conditions.

Lyophilized formulations of proteins can be stable at ambient temperatures for extended periods; therefore, ProLease technology takes advantage of the superior stability of lyophilized protein formulations by encapsulating the protein in the solid state. One of the main reasons for the loss of protein integrity and stability during emulsion-based encapsulated processes is that the protein is encapsulated in the aqueous state. In the solid state, water, a reactant in many protein degradation pathways, is minimized, molecular mobility is reduced, and the kinetics of the degradative reactions are retarded significantly. Additionally, there is the opportunity to add excipients to enhance the stability of the protein during the lyophilization process and for storage stability. Stabilizing strategies include the addition of salting-out agents, sugars, and the formation of reversible metal-protein complexes. In a nonaqueous encapsulation process such as ProLease, proteins are less prone to denaturation and, unlike emulsion-based encapsulation, there are no destabilizing oil-water interfaces.

III. THE PROLEASE ENCAPSULATION PROCESS

The ProLease encapsulation process is outlined in Figure 1. The first step in the ProLease process is the production of the lyophilized protein (or other macromolecule) powder. A liquid formulation of the protein, containing stabilizing additives or excipients, is fed into an atomizing nozzle and sprayed into liquid nitrogen. The droplets freeze instantaneously as they come into contact with the liquid nitrogen. In the small-scale version of the ProLease process, an ultrasonic nozzle is used to atomize the liquid formulation, whereas in the commercial (PL-process) process, the atomization occurs through an air atomizer. The frozen droplets are then lyophilized to produce a friable lyophilized powder. This spray-freeze-drying process is used rather than conventional bulk lyophilization because it provides the ability to control the morphology and friability of the lyophilized powder—two key determinants of the diameter of the encapsulated drug particle. The lyophilization conditions are selected to minimize the residual moisture content of the powder without compromising the integrity of the protein. The lyophi-

Copyright © 2003 Marcel Dekker, Inc.

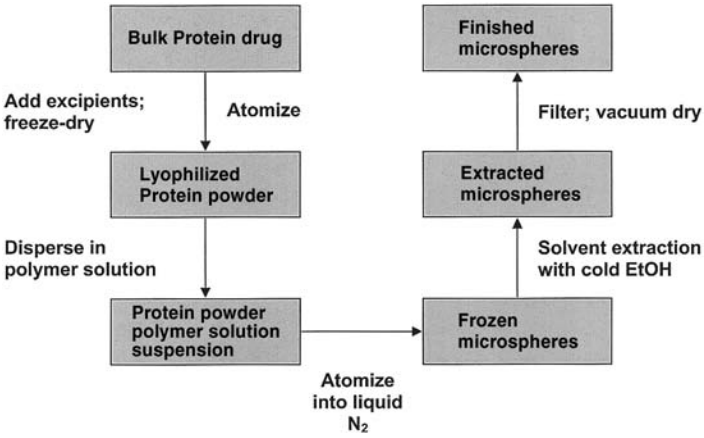


Figure 1 ProLease manufacturing process steps.

lized powder is harvested and stored at −80°C until the microsphere encapsulation step.

To encapsulate the protein powder in the polymer matrix, the poly(D,L-lactide-coglycolide) (PLG) polymer is dissolved in a solvent such as methylene chloride, ethyl acetate, or any other good solvent for the polymer. The lyophilized protein powder is added to the polymer solution and dispersed (by sonication or high-pressure homogenization) to create a uniform suspension of the powder in the polymer solution. The suspension particle size achieved after the dispersion is an important variable that significantly affects the initial release kinetics of the microsphere formulation. The encapsulated drug particle size achieved depends on the ability of the dispersion equipment to break up the friable lyophilized powder. The suspension is atomized to form droplets; these droplets are the precursors of the final microsphere product.

In the small-scale process the suspension is atomized through an ultrasonic nozzle into a receiving vessel containing frozen ethanol overlaid with liquid nitrogen. The droplets freeze in this cryogenic environment and settle on top of the layer of frozen ethanol. In the commercial process, the walls of the spray chamber are prewetted with liquid nitrogen and then the homogenized dispersion of protein particles in PLG/methylene chloride solution is fed under pressure to an atomizer at the top of the spray chamber. The dispersion mixes with nitrogen gas in the atomizer and the fine droplets sprayed from the atomizer freeze upon exiting the atomizer nozzle.

Next, in the extraction step, ethanol extracts methylene chloride from the microspheres. Ethanol is completely miscible with methylene chloride, the latter

Copyright © 2003 Marcel Dekker, Inc.

partitions into the ethanol phase causing the polymer to precipitate, transforming the suspension droplets into microspheres. In the laboratory-scale process, the liquid nitrogen is allowed to boil off and the vessel of frozen ethanol and frozen droplets is transferred to a freezer at −80°C. The ethanol melts and the frozen droplets settle to the bottom of the vessel. Extraction occurs in the commercial process, by transfer of the liquid nitrogen slurry from the spray chamber into an extraction tank containing cold ethanol. The microspheres are collected by filtration and vacuum-dried to produce a free-flowing powder. The bulk microspheres may be sieved to facilitate injectability before filling, sealing, and crimping in glass vials.

IV. STERILIZATION

Aseptic production of protein-containing microspheres at a commercially viable scale under cGMP poses a whole series of challenges. In addition to maintaining the integrity of the encapsulated protein through the scaled-up process, the in vivo release performance must also be identical to the development or laboratory-scale process. The ProLease process was scaled up to ensure that the commercial product was sterile and had the desired performance characteristics that were defined using the small-scale laboratory process. The unit operations in the small-scale process were maintained in the commercial process, but where the laboratory scale equipment could not be scaled up, appropriate equipment substitutions were made. For example, the dispersion of the lyophilized protein powder in the polymer solution is achieved by the use of an ultrasonic probe in the laboratory-scale process. This type of sonicating probe could not easily be scaled up to the commercial scale. Instead, the dispersion step in the commercial process utilizes a high-pressure homogenizer. Statistical experimental design was used to identify the critical operating parameters and the effect on a pharmacokinetic parameter such as C_{max} was determined in a rat model.

Manufacturing sterile protein microsphere products requires the use of some innovative approaches to address the issue of sterility. The microsphere product cannot be autoclaved because the high temperatures required will destroy the polymer and protein. Gamma irradiation may be an option, but exposure of PLG to gamma irradiation has been shown to affect the molecular weight of the polymer and may cause degradation of the encapsulated protein. The use of isolation technology enables production of the microsphere product in an aseptic environment [4]. Isolators contain half suits and/or gloves that give the operator access to the isolator without exposing the product to the operator. The isolator is decontaminated with vapor-phase hydrogen peroxide and optimum aeration times should be selected for each protein to minimize the risk of protein oxidation if one is exposed to high levels of residual peroxide. Solutions are filtered into the

Copyright © 2003 Marcel Dekker, Inc.

isolator using 0.22-μm filters, and solid components are autoclaved or gamma irradiated and introduced into the isolator aseptically using rapid-transfer ports (RTPs). All the production steps including vial filling occur in an isolator, and coupled with the appropriate environmental monitoring program, the microsphere product is manufactured with a high degree of sterility assurance. The first approved long-acting formulation of a therapeutic protein, Nutropin Depot® (Genentech Inc., South San Francisco, CA), is manufactured using the ProLease process.

V. ADMINISTRATION AND DRUG RELEASE

The microspheres may be administered by subcutaneous or intramuscular injection. Just before administration, microsphere powder is dispersed in a viscous aqueous diluent and delivered with a hypodermic needle. The encapsulated drug is released by a mechanism that depends on dissolution of the drug, diffusion of the dissolved drug out of the microspheres, and hydrolysis and weight loss of the polymer to create pores for continuous release of the dissolved drug from the microsphere matrix (Fig. 2). The release profile of the encapsulated drug is characterized by at least two distinct phases (Fig. 3). An initial release phase occurs immediately after the microspheres are hydrated and is a result of dissolution of drug particles on the surface of the microspheres or particles that have access to the surface via micropores that are formed in the microsphere matrix during fabrication. This release phase is affected by the solubility of the drug,

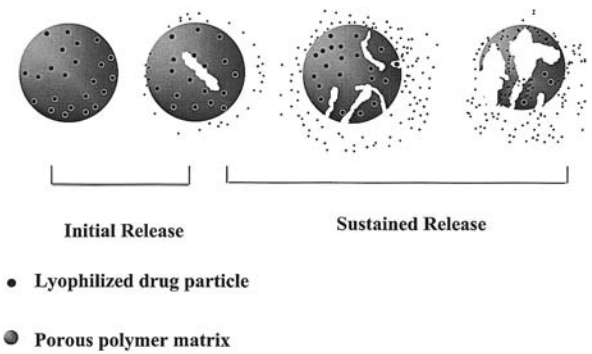


Figure 2 Release of encapsulated drug particles from PLG microspheres. The initial release phase is due to dissolution and diffusion of drug at or near the surface of microspheres. The sustained-release phase is due to polymer mass loss and degradation, creating pores for the continuous release of encapsulated drug particles.

Copyright © 2003 Marcel Dekker, Inc.

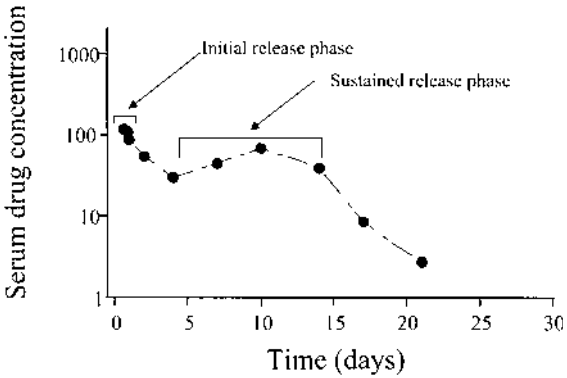


Figure 3 In vivo serum concentration profile of an encapsulated protein drug.

the drug load, the porosity or density of the microspheres, the encapsulated drug particle size, and the polymer (to a lesser extent). If the glass transition temperature of the hydrated microspheres is lower than the temperature at the injection site, the polymer may plasticize and the microsphere porosity may be reduced significantly. When this occurs, any subsequent release depends on hydrolysis of the polymer and dissolution of soluble oligomers to create new channels for drug to dissolve and diffuse out of the microspheres. A lag phase where little or no drug is released is sometimes observed when the hydrolysis and dissolution of the polymer is not initiated until well after the initial drug dissolution/diffusion is over. This may occur if the PLG polymer used is relatively hydrophobic, the polymer matrix is very dense with few channels for release, or the drug is localized within the center of a dense polymer matrix instead of being distributed throughout the microsphere matrix.

The chemical properties of the polymer have a significant effect on the onset and duration as well as the drug concentrations achieved during the sustained-release phase. The ratio of lactide:glycolide affects the hydrophilicity of the polymer and, therefore, the rate of water uptake and the onset of polymer hydrolysis. The polymer molecular weight and end-group chemistry also affect polymer degradation. The higher the molecular weight, the longer the polymer persists and, therefore, the longer the duration of release. The end-group chemistry (i.e., acid versus ester) affects the hydrophilicity of the polymer and, therefore, the rate of hydrolysis and degradation [5].

In vitro release assays that measure the kinetics of protein release from microspheres often do not correlate with observed in vivo performance. It is therefore, not advisable to rely on in vitro release assays as predictors of in vivo performance of microsphere formulations containing protein [6]. Characterizing

Copyright © 2003 Marcel Dekker, Inc.

the in vivo release kinetics from the microspheres or pharmacokinetics of the drug after injection requires an appropriate animal model. When a human protein is introduced into a nonprimate animal, there is usually a strong immune response to the presence of a foreign protein and the production of antibodies interferes with immunoassays that are used to determine serum drug concentrations [7]. The development of an immune-suppressed rat model overcomes the issue of interfering antibodies and allows the formulation to be optimized to meet the desired release kinetic criteria.

VI. CONCLUDING REMARKS

We have demonstrated with the ProLease technology that it is possible to overcome the hurdles discussed in this chapter and develop a cGMP process at commercial scale that produces aseptic product.

REFERENCES

1. H Okada, T Heya, Y Ogawa, T Shimamoto. One-month release injectable microcapsules of a luteinizing hormone-releasing hormone agonist (leuprolide acetate) for treating experimental endometriosis in rats. J Pharmacol Exp Ther 244:744–750, 1988.
2. Okada, H. One and three-month release injectable microspheres of the LH-RH superagonist leuprorelin acetate. Adv Drug Del Rev 28:43–70, 1997.
3. WR Gombotz, MS Healy, LR Brown. Very low temperature casting of controlled release microspheres. Enzytech, 1991.
4. M Tracy. Development and scale-up of a microsphere protein delivery system. Biotech Prog 14:108–115, 1998.
5. MA Tracy, KL Ward, L Firouzabadian, Y Wang, N Dong, R Qian, Y Zhang. Factors affecting the degradation rate of poly(lactide-co-glycolide) microspheres in vivo and in vitro. Biomaterials 20:1057–1062, 1999.
6. OL Johnson. Development of biodegradable microsphere formulations of proteins, peptides and small molecules. AAPS Workshop: Assuring Quality and Performance of Sustained and Controlled Release Parenterals. Washington, DC: AAPS, 2001.
7. HJ Lee, G Riley, O Johnson, JL Cleland, N Kim, M Charnis, L Bailey, E Duenas, A Shahzamani, M Marion, AJ Jones, SD Putney. In vivo characterization of sustained release formulations of human growth hormone. J Pharmacol Exp Ther 281: 1431–1439, 1997.

Copyright © 2003 Marcel Dekker, Inc.

57

Sucrose Acetate Isobutyrate (SAIB) for Parenteral Delivery

Arthur J. Tipton
Southern BioSystems, Birmingham, Alabama, U.S.A.

I. INTRODUCTION

This chapter discusses the use of sucrose acetate isobutyrate (SAIB) and similar materials for parenteral drug delivery applications. SAIB is a well-known food additive [1] approved in over 40 countries for use as an alternative to brominated vegetable oil in soft drinks, where it stabilizes emulsions, primarily by acting as a densifier for the citrus oil flavorings. SAIB is a very hydrophobic, fully esterified sucrose derivative, at a nominal ratio of six isobutyrates to two acetates, as shown in Figure 1. The material is manufactured by Eastman Chemical Company as a mixed ester, and the resulting mixture does not crystallize but exists as a very viscous liquid. The unusual properties of SAIB, specifically high hydrophobicity and high viscosity, can be exploited to provide sustained drug delivery for periods ranging from a few hours to several weeks. A number of approaches to drug delivery are disclosed in U.S. patent "High-Viscosity Liquid Controlled-Delivery System" [2] owned by Southern BioSystems, Inc., a subsidiary of the Durect Corporation. In the simplest case, the high-viscosity SAIB is formulated as a low-viscosity liquid by mixing with a pharmaceutically acceptable solvent [3]. The drug to be delivered is dissolved or dispersed in the SAIB/solvent solution for subsequent injection subcutaneously or intramuscularly. If a water-soluble solvent such as ethanol is chosen, the solvent will diffuse out of the injected volume leaving a viscous depot of SAIB and drug. The use of a more hydrophobic solvent such as benzyl benzoate gives a less viscous depot with slower solvent diffusion. Sustained drug release occurs over a period from several hours to several weeks by diffusion. The duration of release is controlled by adjusting a num-

Copyright © 2003 Marcel Dekker, Inc.

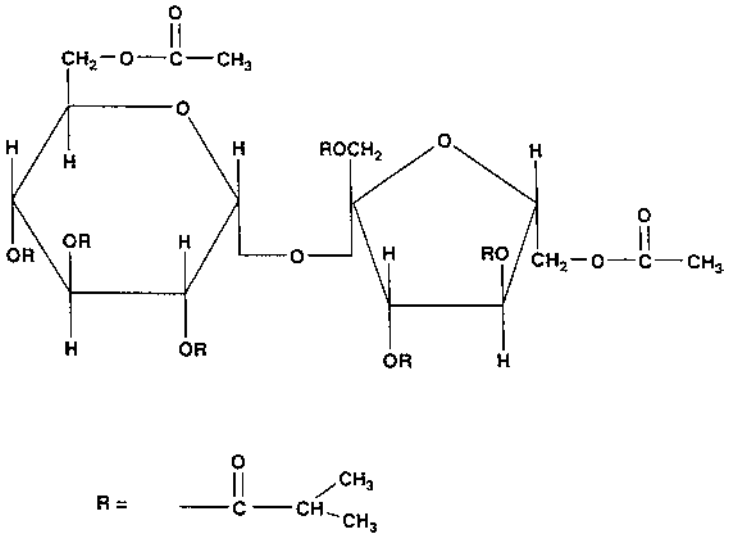


Figure 1 Structure of SAIB.

ber of parameters such as drug loading, type and amount of solvent, and type and amount of additive, if any. Additional U.S. patents have been issued covering medical device applications [4] and the delivery of certain peptides [5]. Worldwide patent applications are filed as well as additional U.S. patent applications.

II. EVOLUTION OF SAIB FOR PARENTERAL DELIVERY

The use of SAIB for parenteral delivery grew from a relationship between Southern BioSystems (SBS) and the Eastman Chemical Company (Eastman). SBS has a strong background in parenteral drug delivery, primarily using technologies based on biodegradable polymers in the polylactide/polyglycolide family. Eastman is a leader in the chemistry of mixed-ester compounds, such as cellulose acetate butyrate, and is a supplier of SAIB. SBS and Eastman began a business and technical relationship in 1993 when Eastman became an investor of SBS. The need in the pharmaceutical industry for an in situ–forming depot (ISFD) system with lower injection viscosity than any available at the time and the remarkable decrease in viscosity with minimal amounts of solvent led to SBS's development of this technology. The controlled-release technology platform is

Copyright © 2003 Marcel Dekker, Inc.

referred to by the trade name Saber™ (sucrose acetate isobutyrate extended release).

III. DEPOT TECHNOLOGIES

The Saber technology fits into the technology area of biodegradable ISFDs [6]. ISFDs compete with preformed systems such as microspheres and implants. Small, injectable, preformed polymer microspheres serve as the basis for long-term drug delivery. The most significant product on the market is Lupron Depot®, the leuprolide acetate microsphere product based on poly(DL-lactide) (PLA), and poly(DL-lactide-coglycolide) (PLG) for the treatment of prostate cancer, endometriosis, and precocious puberty. Implants are formed as cylindrical rods, and the most well-known example is Zoladex®, again prepared from PLG and used in the treatment of prostate cancer with the delivery of goserelin. An inherent drawback of all these preformed delivery systems is administration. Implants are placed subcutaneously (SC) using a relatively large-bore needle (10–16 gauge). The microspheres are injected using smaller-bore needles, but the need for an intramuscular (IM) injection and dispersion in an aqueous vehicle are drawbacks. The use of ISFDs has evolved to address issues related to difficulty of injection, but they also have advantages in terms of manufacturing ease, higher drug loading, local anatomical placement, and clinical acceptance.

Several organizations have recognized the drawbacks associated with preformed depot delivery systems and have begun research into systems that can be easily injected and then, after injection, undergo a change to form a depot system. These broadly fall into aqueous-based systems and systems using organic solvents. Aqueous-based systems often have a disadvantage in that the high percentage of water results in rapid drug delivery. Polymer-based organic solvent systems have been described for the delivery of several drugs and offer the potential of delivery for up to 3 months. The main advantage of the Saber system over the polymer-based systems is a lower solution viscosity and relatively low solvent content that translates to easier injectability. Other key advantages are lower depot viscosity that allows for easier diffusion of high-molecular-weight drugs such as proteins, higher hydrophobicity compared to PLGs providing better protection for certain drugs, and lower cost.

IV. SABER TECHNOLOGY

The Saber platform is generally used in parenteral applications as a three- or four-component system of SAIB, solvent, drug, and additive. The SAIB and sol-

Copyright © 2003 Marcel Dekker, Inc.

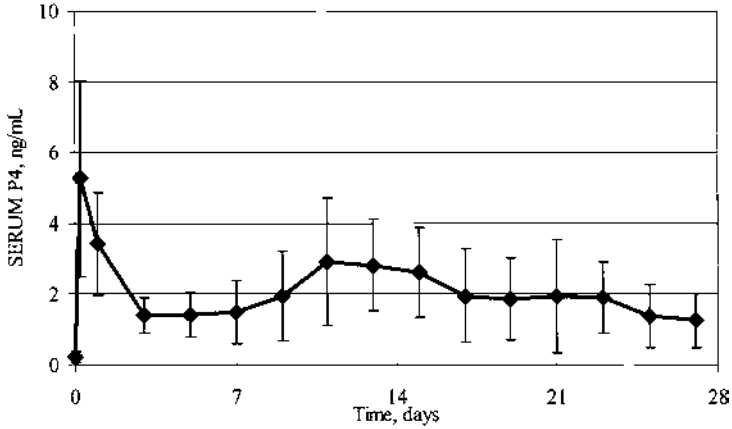


Figure 2 Release of progesterone from an intramuscular route of administration in the horse [7].

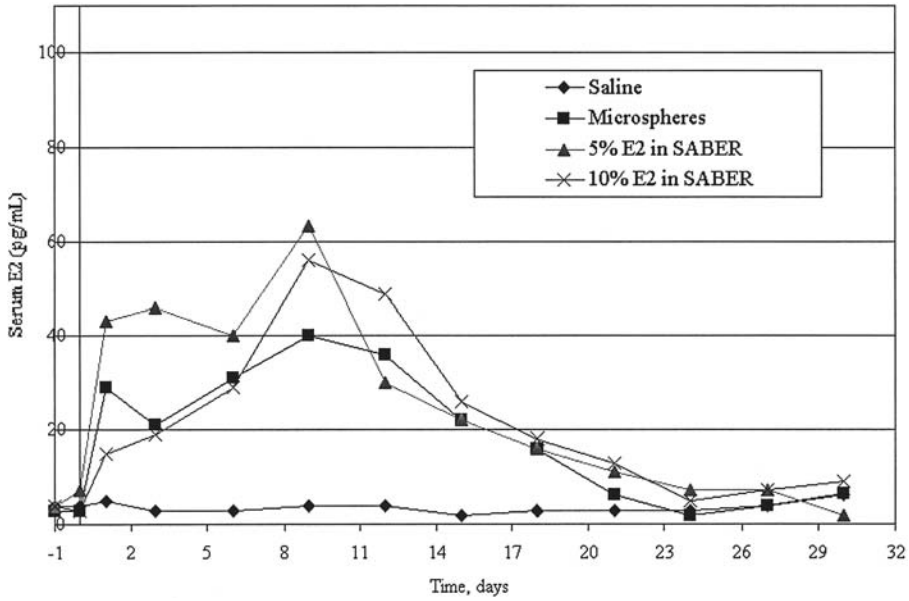


Figure 3 Release of estradiol from an intramuscular administration in the horse [8].

Copyright © 2003 Marcel Dekker, Inc.

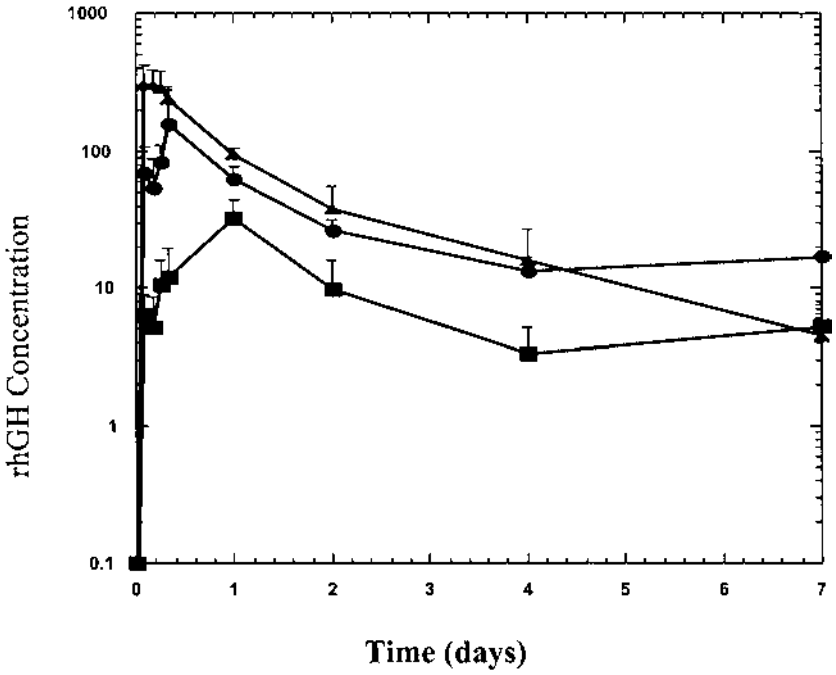


Figure 4 Release of rhGH in rats [9]. ▲, 1%PLA w/formulation 20 mg/mL rhGH, 2 mg/mL sucrose, 0.05 %w/v Tween 20, $n = 5$; ■, 10%PLA w/formulation 20 mg/mL rhGH, 2 mg/mL sucrose, 0.05 %w/v Tween 20, $n = 3$; ●, 10%PLA w/formulation, 20 mg/mL rhGH, 5 mg/mL sucrose, 0.05 %w/v Tween 20, $n = 5$.

vent are mixed to form a solution, and the drug is dissolved or dispersed in this solution. In some applications, an additive is used to affect release kinetics, drug stability, or other performance parameters. This combination is formulated as a low-viscosity fluid that is administered either subcutaneously or intramuscularly. Upon injection the hydrophobic SAIB forms a high-viscosity depot from which drug slowly diffuses. SAIB degradation follows drug release.

Although the Saber system had not been evaluated in a clinical study as of 2001, it has been evaluated in a large number of in vitro and in vivo studies. For in vitro analysis, single drops of formulation are place in phosphate-buffered saline (PBS), incubated, and samples removed at designated time intervals and analyzed for drug. More than 20 drugs have been evaluated for in vivo release kinetics. These studies have been in seven species and over 2500 total animals.

Copyright © 2003 Marcel Dekker, Inc.

Durations of release of 24 h–4 weeks have been published, as shown in Figures 2–4, and unpublished data show release durations of 12 weeks.

There have been no unusual obstacles in developing the Saber system. There are, however, a great number of experimental variables to evaluate including drug properties and loading, solvent type, SAIB-to-solvent ratio, additive type, and additive concentration. To fully evaluate such a large matrix is difficult, and statistical experimental design will be increasingly used in the future to make efficient progress.

V. MANUFACTURE

Saber-based products are manufactured in a liquid mix-and-fill process using conventional tanks and stirrers. For dispersed drugs, particle size of the drug must be controlled, and particle size reduction is done by milling. Homogenizers have been used to disperse some of the drug suspensions.

Because the Saber technology is manufactured as a mix-and-fill liquid formulation, there have been no specific scale-up problems. Two issues that must be considered are transferring the high-viscosity raw material SAIB and the use of organic solvents. The use of solvents imposes certain limits on contact surfaces and requires particular attention in selecting tubing and seals.

VI. APPLICATIONS

A wide range of drugs are compatible for use with the Saber system, essentially all parenteral applications in which long-term sustained delivery is desired. Table 1 shows a partial list of drugs evaluated to date. Southern BioSystems, Inc. has published data describing applications with anticancer agents [10], antigens [11], anesthetics [12], steroids [8], LHRHs [13], and therapeutic proteins [14]. As an ISFD, Saber can combine device and drug delivery functions, for example being injected into a tumoral supply artery where it will occlude blood flow and deliver an anticancer agent. The available data demonstrate release in vivo from 1 day to 1 month, and more recent data show release of greater than 2 months.

Southern BioSystems, Inc. has publicly announced business collaborations with Purdue Pharma, LLC, and AstraZeneca, both with undisclosed drugs. SBS has published jointly with Genentech data demonstrating application of the Saber system to achieve sustained release of human growth hormone and vascular endothelial growth factor, and with Thorn BioScience on veterinary uses including

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Compounds Evaluated in Saber Technology (published and presented data)

In vivo	In vitro
Progesterone	Methylene blue
Estradiol	BSA
Deslorelin	Chlorhexidine
a-FGF	Doxycycline
Heparin	Diclofenac
LHRH	Flurbiprofen
Avorelin	Naproxen
GRP	Theophylline
SeM protein	Bupivacaine
VEGF	Taxol
hGH	5-FU
	Doxorubicin
	Deslorelin
	Acetaminophen
	AZT
	ddC

the delivery of steroids and reproductive peptides. Some of these programs are in advanced animal testing progressing toward human clinical trials.

VII. SAFETY

While SAIB has an extensive safety profile including carcinogenicity, mutagenicity, and teratology studies, it has yet to be used in an approved drug product. A full safety protocol including metabolic fate is being performed. Based on preliminary data, no negative results are expected, but the package has yet to be submitted in support of an IND or NDA. As most Saber formulations also use organic solvents, the safety and use of those materials must also be justified to regulatory agencies.

VIII. FUTURE DIRECTIONS

Southern BioSystems, Inc. is now working to develop new materials with properties similar to those of SAIB to be used in the Saber system and to expand the choice of solvents to include PEG and glycerol [15].

Copyright © 2003 Marcel Dekker, Inc.

IX. CONCLUDING REMARKS

Data have been published describing scale-up of a Saber product to 12,000 doses, including the manufacturing methods, methods for sterilization, QC characterization, and stability [16]. As more products work toward human clinical testing, this database will be expanded for a number of drug formulations.

REFERENCES

1. RC Reynolds, CI Chappel. Sucrose acetate isobutyrate (SAIB): historic aspects of its use in beverages and a review of toxicity studies prior to 1988. Food Chem Toxicol 36:81–93, 1988.
2. AJ Tipton, RJ Holl. High-viscosity liquid controlled-delivery system. US patent 5,747,058, 1998.
3. DA Smith, AJ Tipton. A novel parenteral delivery system. Pharm Res 13:300, 1996.
4. AJ Tipton. High-viscosity liquid controlled-delivery system as a device. US patent 5,968,542, 1999.
5. PJ Burns, JW Gibson, AJ Tipton. Compositions suitable for controlled release of the hormone GnRH and its analogs. US patent 6,051,558, 2000.
6. AJ Tipton, RL Dunn. In situ gelling formulations. In: J Senior, M Radomsky, eds. Sustained Release Injectable Products. Buffalo Grove, IL: Interpharm Press, 2000.
7. SA Sullivan, JW Gibson, PJ Burns, L Franz, EL Squires, DL Thompson, AJ Tipton. Sustained release of progesterone and estradiol from the Saber delivery system: in vitro and in vivo release rates. Proc Int Symp Control Rel Bioact Mater 25:653–654, 1998.
8. CA Johnson, DL Thompson, SA Sullivan, JW Gibson, AJ Tipton, BW Simon, PJ Burns. Biodegradable delivery systems for estradiol: comparison between poly(DL-lactide) microspheres and the Saber delivery system. Proc Int Symp Control Rel Bioact Mater 26:74–75, 1999.
9. FW Okumu, A Daugherty, L Dao, PJ Fielder, D Brooks, S Sane, S Sullivan, AJ Tipton, JL Cleland. Evaluation of the Saber delivery system for sustained release of growth hormone: formulation design and in vivo assessment. Proc Int Symp Control Rel Bioact Mater 28:2001 (abstract 6211).
10. SA Sullivan, RM Gilley, JW Gibson, AJ Tipton. Delivery of Taxol and other antineoplastic agents from a novel system based on sucrose acetate isobutyrate. Pharm Res 14:291, 1997.
11. J Nally, S Artiushin, A Sheoran, J Timoney, JW Gibson, SA Sullivan, R Gilley, B Simon, PJ Burns. Induction of mucosal IgA specific for SeMF3 of *Streptococcus equi* with intranasal vaccination using a sucrose acetate isobutyrate–based delivery system. Proc Int Symp Control Rel Bioact Mater 26:1168–1169, 1999.
12. SA Sullivan, JW Gibson, AJ Tipton. Sustained release of bupivacaine from the Saber delivery system. Presented at the AAPS Annual Meeting and Exposition, San Francisco, Nov. 15–19, 1998.
13. J Fleury, EL Squires, R Betschart, JW Gibson, SA Sullivan, AJ Tipton, PJ Burns.

Copyright © 2003 Marcel Dekker, Inc.

Evaluation of the Saber delivery system for the controlled release of deslorelin for advancing ovulation in the mare: effects of formulation and dose. Proc Int Symp Control Rel Bioact Mater 25:657–658, 1998.
14. JL Cleland, L OluFumni Johnson, S Darling, AJ Tipton, GM Zentner, SA Sullivan, JW Gibson, FW Okumu. Depot delivery of proteins in the new millennium: from microspheres to injectable gels. Presented at the 6th European Symposium on Controlled Drug Delivery, Noordwijk Aan Zee, The Netherlands, April 12, 2000.
15. JW Gibson, SA Sullivan, JC Middleton, AJ Tipton. High viscosity liquid controlled delivery system and medical or surgical device. WO/0115734 A2, 2001.
16. AJ Tipton. Peptide delivery from an in situ gelling system based on sucrose acetate isobutyrate. Invited lecture at the AAPS Annual Meeting and Exposition, New Orleans, Nov. 14–18, 1999.

Copyright © 2003 Marcel Dekker, Inc.

58
Stealth Technology

Frank Martin and Tony Huang
ALZA Corporation, Mountain View, California, U.S.A.

I. INTRODUCTION

Since their discovery over 35 years ago, liposomes have been applied to the delivery of a wide range of drugs by virtually every route of administration [1,2]. This chapter will discuss intravenous (IV) liposomes that use Stealth® technology to target their contents to specific sites of disease. Particular attention will be paid to Doxil® (doxorubicin HCl liposome injection), also known as Caelyx™ in countries outside the United States.

Liposomes are vesicular "sacs" resembling tiny cells. As in cells, a thin but durable lipid membrane separates an internal aqueous volume from the external medium. Water-soluble drugs can be encapsulated in these internal compartments, while water-insoluble drugs can be incorporated in the hydrophobic region of the membrane. Depending on the production process used, each vesicle can contain a single membrane (unilamellar) or several layers of membrane (multilamellar). Typical liposome sizes range from 0.05 to several microns.

The prospects of targeting liposome-encapsulated drugs to sites of disease, such as tumors, created considerable excitement in the 1960s and 1970s. Although early liposomal formulations of antitumor drugs, such as doxorubicin, were shown to reduce toxicities, they were no more active than the unencapsulated drug [3]. This lack of improved antitumor activity of conventional doxorubicin liposomes relative to the unencapsulated drug was subsequently attributed to two related biological responses. First, the liposomes were unstable in blood and released up to 50% of their contents as a consequence of rapid binding (opsonization) of plasma proteins [4]. Second, liposomes that survived destabilization in

Copyright © 2003 Marcel Dekker, Inc.

blood were rapidly sequestered by fixed macrophages residing in the liver and spleen (the mononuclear phagocyte system, MPS) [5]. Once internalized by macrophages, the liposomes were destroyed. This combination of instability and MPS uptake restricted the opportunity for "true" targeting.

Considerable progress was made during the 1970s and 1980s in engineering liposomes to circulate longer in the blood and remain intact while doing so. Small (<50 nm) liposomes composed of high-phase transition lipids and cholesterol were found to resist degradation in blood and to circulate for several hours in rodents [6] and in human cancer patients [7]. Circulation times were significantly improved when glycolipids were introduced into liposome formulations [8,9]. Moreover, prolonged circulation times were highly correlated with improved distribution of liposomes to implanted tumors in mice [10], supporting the theory that reducing the rate of MPS uptake and increasing circulation time would allow IV-injected liposomes to access systemic tumors (Fig. 1).

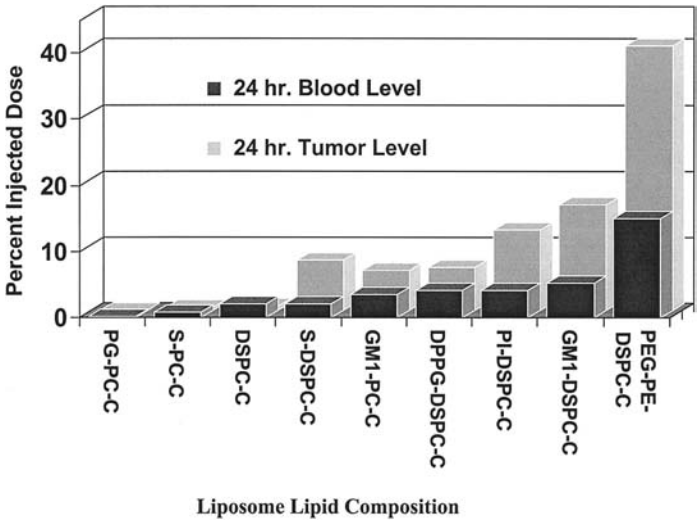


Figure 1 Uptake of radiolabeled liposomes (expressed as a percent of the total dose of radioactivity injected) in subcutaneously implanted solid tumors in mice 24 h after tail vein injection of various formulations. All liposomes were of equivalent size (circa 100 nm). PG, phosphatidylglycerol; PC, phosphatidylcholine; C, cholesterol; DSPC, distearoylphosphatidylcholine; S, sphingomyelin; GM_1, brain-derived ganglioside; DPPG, dipalmitoylphosphatidylglycerol; PI, hydrogenated phosphatidylinositol; PEG-PE, methylpolyethylene glycol derivative of distearoylphosphatidylethanolamine [45]. (Adapted from Ref. [10]).

Copyright © 2003 Marcel Dekker, Inc.

II. STEALTH LIPOSOMES

The most promising results of liposome modification were achieved by grafting polymer groups to the liposome surface. One example of this modification is represented by Doxil, a "pegylated" formulation of doxorubicin. This type of liposome contains surface-grafted segments of the hydrophilic polymer methoxy-polyethylene glycol (MPEG). A schematic representation of a Stealth liposome, not drawn to scale, is presented in Figure 2.

A. Design Features

The critical design features of the Stealth liposome include:

Polyethylene glycol (Stealth polymer) coating: Reduces MPS uptake and provides long plasma residence times and plasma stability.

Low-permeability lipid matrix and internal aqueous buffer system: Provides high drug loading and stable encapsulation, i.e., drug retention during residence in plasma.

Average diameter of approximately 100 nm: Balances drug-carrying capacity and circulation time, and allows extravasation through endothelial defects/gaps in tumors.

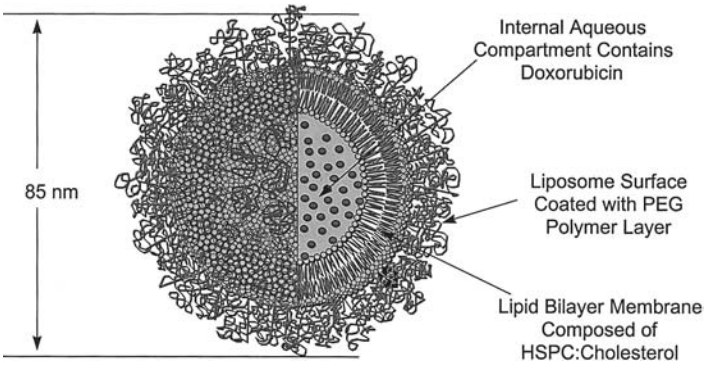


Figure 2 Schematic representation of a Doxil liposome. A single lipid bilayer membrane composed of hydrogenated soy phosphatidyl choline (HSPC) and cholesterol separates an internal aqueous compartment from the external medium. Doxorubicin is encapsulated in the internal compartment. Polymer groups (linear 2000-dalton segments of polyethylene glycol) are grafted to the liposome surface (although not shown, the polymer also extends from the inner monolayer of the membrane).

Copyright © 2003 Marcel Dekker, Inc.

1. Polymer Coating

The long residence times and stability of Doxil in plasma are believed to be related to a steric stabilization effect provided by MPEG; that is, the extension of the MPEG molecules from the liposome surface forms a protective hydrophilic layer that prevents interaction of plasma components with the liposomes [11–13]. X-ray diffraction analyses of liposomes containing MPEG lipids of molecular weights ranging from 350 to 5000 daltons indicate that the range and magnitude of the steric effect increase both with increasing MPEG-lipid concentration and MPEG molecular weight. The extension length of the MPEG from the liposome surface at maximum MPEG-lipid concentration depends strongly on the size of the MPEG: less than 35 angstroms for PEG-750, approximately 65 angstroms for PEG-2000, and 115 angstroms for PEG-5000 [14].

The biological impact of MPEG incorporation into liposomes correlates well with physicochemical observations. The circulation time of Stealth liposomes is influenced by the relative amount of MPEG-modified lipid present in the liposome and the molecular weight of the MPEG segment. Optimal circulation times require between 2.5 mole% (m%) and 20 m% of MPEG-modified lipid and a polymer molecular weight between 2000 and 5000 daltons [15–17]. Other hydrophilic polymers grafted to liposomes, including poly(acryloylmorpholine), poly(vinylpyrrolidone), and poly(2-oxazoline), have also been reported to increase circulation time [18–21].

2. Stable Drug Encapsulation

Stable drug encapsulation is essential for successful targeting of liposomes—any drug released while liposomes circulate in the bloodstream would detract from the amount delivered to disease sites. Stealth liposomes may circulate in blood for up to a week after injection. Ensuring the stability of liposomes exposed to such dynamic conditions for so long a period can be challenging. Many drugs that can be encapsulated into liposomes in vitro quickly leak when exposed to plasma components.

In the case of Doxil, the bulk of the membrane is composed of a fully saturated phospholipid that assumes a liquid crystalline morphology at body temperature. Membranes made of this type of lipid are more resistant to leakage than ones composed of less saturated phospholipid varieties [22]. The internal buffer system used to load and retain doxorubicin in the liposomes is also critical to the stability of the system [23]. Indeed, nearly all of the doxorubicin measured in the plasma of a group of cancer patients given a single dose of Doxil was liposome-encapsulated (Fig. 3) [24]. Similar results have been reported in pharmacokinetic studies conducted in rodents [25].

Copyright © 2003 Marcel Dekker, Inc.

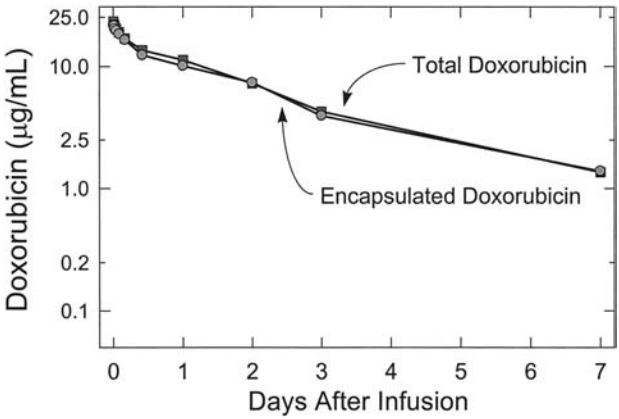


Figure 3 Clearance over a 1-week period of total versus encapsulated doxorubicin after a single 50 mg/m^2 dose of an early formulation of Doxil (containing 150 nm ammonium sulfate) in 14 cancer patients. Data points represent mean values ± standard deviation. (Adapted from Ref. [24]). The separation method has been described by Druckmann and colleagues [73].

3. Liposome Size and Extravasation in Tumors

The size of the liposome is critical to the effective delivery of encapsulated drugs to disease sites. If the liposomes are too large, extravasation is not possible. Conversely, if the liposomes are too small, the amount of drug delivered to the tumor (the drug payload) will be inadequate, as the aqueous volume available for drug encapsulation in each liposome decreases dramatically with decreased liposome size.

Most solid tumors exhibit unique pathoanatomical features, such as extensive angiogenesis, hyperpermeable and defective vasculature architecture, impaired lymphatic drainage, and greatly increased production of mediators that enhance vascular permeability [26–28]. Liposomes extravasate in solid tumors through defects present in the endothelial barriers of newly forming blood vessels.

The rate and extent of extravasation in solid tumors are related to the size and plasma residence times of the liposome. Particles with an average diameter greater than 600 nm do not extravasate at all. For particles with diameters below 600 nm, the rate of extravasation appears to increase with smaller diameters [29,30].

In preclinical studies of mice treated with Stealth liposomes containing colloidal gold particles as markers, microscopic examination of C-26 colon carcinomas and Kaposi sarcoma (KS)-like lesions revealed high concentrations of

Copyright © 2003 Marcel Dekker, Inc.

liposomes in interstitial areas surrounding tumor capillaries [31–33]. These findings suggest that Stealth liposomes circulate for a sufficient period of time and are small enough to extravasate through the capillaries supplying tumors. After being trapped in tumor tissues, Stealth liposomes gradually release the encapsulated drug, which then enters the tumor cells [34].

B. Other Applications of Stealth Technology

The design features of the Stealth liposome (stability in plasma, increased plasma residence time, and extravasation in areas of enhanced vascular permeability) have led researchers to pursue other applications of the technology. Researchers are studying the use of Stealth liposomes to deliver encapsulated drugs to areas of infection and inflammation, and to function as intravascular reservoirs for unstable therapeutic agents.

Preferential localization of long-circulating liposomes at sites of infection and inflammation has been demonstrated in a variety of experimental models and human clinical trials. Anti-infective agents encapsulated in liposomes provided improved therapy, relative to that provided by unencapsulated drugs [35–38]. In animal models, the extent of liposome localization at sites of infection was positively, linearly related to the area under the blood concentration time curve (AUC) of the liposome formulations, highlighting the positive effect of the PEG coating [39]. Gamma scintigraphy has been used to successfully image sites of inflammation after injection of long-circulating liposomes containing technetium-99m in animal models and human patients [37,40–42].

Another potential application of Stealth liposomes is their use as intravascular microreservoirs for labile therapeutic agents; a sustained plasma level can be achieved as the drug is gradually released from the liposomes during their residence time in the circulatory system. This may result in enhanced bioavailability relative to oral, transdermal, and subcutaneous routes of delivery.

C. Production Methodology

A flow chart illustrating the key steps of the Stealth liposome manufacturing process is presented in Figure 4. Phospholipids, including the MPEG-based Stealth coating, are first dissolved in a water-miscible organic solvent, such as ethanol. This solution is injected into an aqueous solution. The organic solvent is diluted by the aqueous solution, and the phospholipid molecules spontaneously arrange themselves to form liposomal structures. At this step (hydration), the liposomes are very large and heterogeneous. The liposome suspension is then put through a size-reduction step to obtain a homogeneous, small-size liposome preparation. Size reduction can be achieved with high-pressure homogenization

Copyright © 2003 Marcel Dekker, Inc.

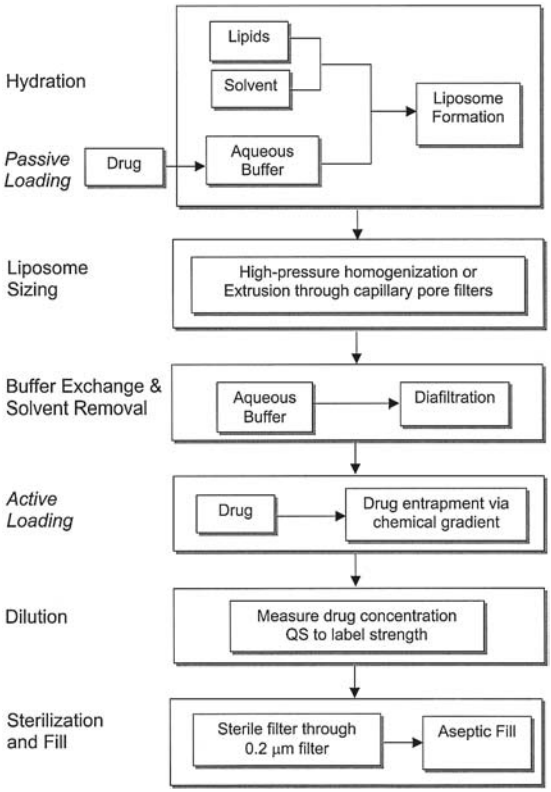


Figure 4 Flow diagram of Stealth liposome production process.

techniques [43] or extrusion through track-etched membranes of defined pore sizes [44].

Therapeutic agents can be loaded into Stealth liposomes at different stages of the process, depending on their physical and chemical properties. For example, the drug can be loaded in the aqueous solution during the hydration step. In this method, referred to as passive loading, liposome formation and drug encapsulation occur at the same time. Alternatively, the drug can be loaded after the liposomes are formed, a process called active loading. This strategy is used in the manufacture of Doxil. In this case, the hydration is done in an ammonium sulfate solution. After size reduction, the extraliposomal ammonium sulfate is removed by diafiltration. Doxorubicin is then added to the liposome preparation. The absence of ammonium sulfate in the extraliposomal phase establishes a chemical gradient that induces the drug to diffuse into the liposomes and become trapped

Copyright © 2003 Marcel Dekker, Inc.

inside. This type of loading is usually more efficient than passive loading. Over 90% of the added drug becomes encapsulated during the loading of Doxil, while typical encapsulation efficiency for passive loading processes ranges from 20% to 40%. After loading, the unencapsulated drug can be removed by diafiltration or ionic exchange methods. The preparation is then sterilized by passage through a 0.2-μm sterilization membrane and filled into final product vials. When needed, the product can be lyophilized for added stability.

The manufacturing process for Stealth liposomal products is relatively complex and usually takes several days to complete. Depending on drug potency, production scale at early clinical development stages varies from a few liters to tens of liters, while commercial scales range from 50 to several hundred liters. Product characteristics (e.g., drug potency, lipid composition, liposome size, percent drug encapsulation, drug-to-lipid ratio, and drug leakage rate) and the analytical methods capable of accurately measuring these characteristics need to be defined early in the development process. Successful process scale-up depends on a thorough understanding of the effects of processing conditions on these characteristics. In general, the manufacturing process for Stealth liposomes is well established, and successful routine production in commercial manufacturing settings has been demonstrated.

D. Clinical Experience

Currently, Doxil is the only approved product utilizing Stealth technology. Clinical pharmacology studies confirm preclinical findings showing that Doxil achieves higher concentrations at tumor sites compared with unencapsulated formulations of doxorubicin [45–49]. Relative to free doxorubicin, Doxil treatment resulted in a 4–16-fold enhancement of drug levels in malignant effusions obtained from three cancer patients [50] and 5–11-fold higher drug levels in KS lesions [51].

Liposomes of the same size and composition as Doxil containing the radioactive tracer ^{111}In-DPTA were injected into a series of cancer patients [52,53]. Gamma scintigraphy performed on these patients revealed substantial uptake of intact liposomes in primary and metastatic tumors in the breast, head and neck, cervix, brain, and pulmonary and cutaneous KS lesions. Serial gamma scintigrams of one patient with AIDS-related KS entered in this trial are presented in Figure 5.

The antitumor activity and tolerability of Doxil have been extensively studied in patients with AIDS-related KS [51,54–60], advanced ovarian cancer [61–65], and breast carcinoma [66]. Currently, Doxil is approved and marketed in the United States and many other countries for the treatment of refractory AIDS-related KS and refractory ovarian cancer.

Copyright © 2003 Marcel Dekker, Inc.

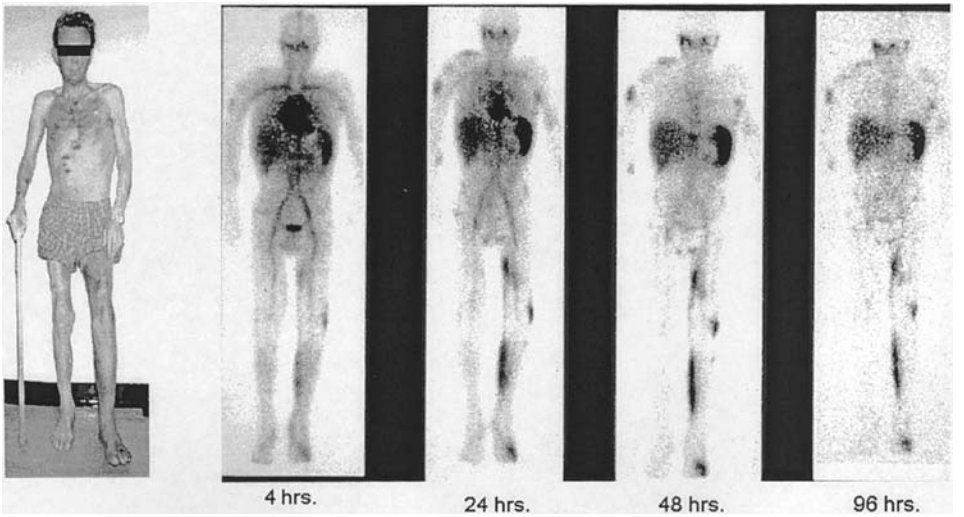


Figure 5 Serial gamma scintigrams of KS patient given ^{111}In-DTPA Stealth liposomes [52,53]. The AIDS-KS patient pictured in the left panel received a single IV injection of liposomes containing ^{111}In-DPTA. Serial scintigrams were obtained for up to 96 h after injection. Note the uptake pattern of the radiolabeled liposomes in the large KS lesions on the patient's left calf and thigh. Little uptake is seen at 4 h; most of the label is present in the blood pool. Peak lesion uptake is seen at the 24- and 48-h time points. A significant amount of the radiolabel remains in the lesion after 96 h. Importantly, this technique reports the location of *intact* liposomes (any of the radiolabel released from liposomes is cleared by the kidneys within a few minutes).

III. FUTURE DIRECTIONS

Active targeting of Stealth liposomes to tumor cells is an area of increasing interest. To achieve active targeting, ligands, such as antibodies and antibody fragments, are chemically tethered to the termini of the PEG chains extending from the liposome surface. In one formulation, a single-chain antibody fragment to HER2, a growth factor receptor overexpressed in a wide range of human epithelial tumors, has been introduced into Doxil [67,68]. In animal models, the anti-HER2-targeted Doxil has been shown to have superior antitumor activity relative to unencapsulated doxorubicin and Doxil [67–69]. Other ligands being explored for targeting of Doxil include vitamins, such as folate, and growth factors, including FGF, VEGF, and EGF [70].

Copyright © 2003 Marcel Dekker, Inc.

Ligand-bearing Stealth liposomes have also been used to affect important biological receptor-binding events. For example, in inflammatory tissues, pegylated liposomes with Sialyl Lewis^x moieties on the surface were shown to effectively inhibit the binding of circulating lymphocytes to selectins expressed on vascular endothelial cells. In a feline myocardial reperfusion model, these liposomes significantly attenuated myocardial necrosis and preserved coronary endothelial functions after a myocardial ischemia/reperfusion challenge [71].

Stealth liposomes also offer a potential vehicle for the delivery of plasmid genes to sites of disseminated disease. MPEG-coated DNA constructs appear to exhibit favorable pharmacokinetic and tumor distribution properties. Unfortunately, the MPEG group appears to interfere with cellular uptake of the liposome-encapsulated DNA. Possible solutions to this classic drug-delivery dilemma have recently been proposed. One such liposome system, termed "PolyVerse™," employs MPEG groups that are designed to detach from the liposome after entry into tumors [72]. The denuded liposomes are then able to bind and enter cells.

IV. CONCLUSIONS AND PERSPECTIVES

Liposomes can be engineered to stably encapsulate doxorubicin and other drugs, to recirculate for periods of several days after IV injection without releasing the drug, to penetrate into tumor tissues, and to release encapsulated drug within the tumor [24]. Moreover, such liposomes can be consistently produced at large scale and have a shelf life typical of other injectable pharmaceutical products.

Doxil received approval in the United States within 5 years of its initial development, a remarkable achievement when compared with the 10-year period typically needed to register a new chemical entity (NCE). Rapid registration of Doxil was due, in part, to the fact that the encapsulated drug was not an NCE. Although liposome encapsulation may introduce differences in tissue distribution and pharmacokinetics, and may affect the safety and efficacy profiles of the drug (positively or negatively), the intrinsic biological activity of the drug is not altered.

The prospects to create additional products based on Stealth technology are promising. Many of the presumed obstacles to the development of liposome pharmaceuticals, such as instability, lack of reproducibility, scale-up difficulties, and high cost of goods, have been overcome. Therapeutic agents that may be delivered by this technology include small molecules, proteins, peptides, oligonucleotides, and plasmid DNA. Future applications of Stealth technology may involve a variety of therapeutic and diagnostic areas, including the delivery of other antineoplastics, antimicrobials, anti-inflammatory drugs, and peptides.

Copyright © 2003 Marcel Dekker, Inc.

ACKNOWLEDGMENT

The authors wish to acknowledge the editorial assistance of Laurie McClain.

REFERENCES

1. AD Bangham. Surrogate cells or Trojan horses: the discovery of liposomes. Bioessays 17:1081–1088, 1995.
2. G Gregoriadis. Engineering liposomes for drug delivery: progress and problems. Trends Biotechnol 13:527–537, 1995.
3. A Gabizon. Liposomal anthracyclines. New Drug Ther 8:431–450, 1994.
4. A Gabizon, R Chisin, S Amselem, S Druckmann, R Cohen, D Goren, I Fromer, T Peretz, A Sulkes, Y Barenholz. Pharmacokinetic and imaging studies in patients receiving a formulation of liposome-associated Adriamycin. Br J Cancer 64:1125–1132, 1991.
5. D Liu, Q Hu, YK Song. Liposome clearance from blood: different animal species have different mechanisms. Biochim Biophys Acta 1240:277–284, 1995.
6. RT Proffitt, LE Williams, CA Presant, GW Tin, JA Uliana, RC Gamble, JD Baldeschwieler. Tumor-imaging potential of liposomes loaded with in-111-NTA: biodistribution in mice. J Nucl Med 24:45–51, 1983.
7. PS Gill, J Wernz, DT Scadden, P Cohen, GM Mukwaya, JH von Roenn, M Jacobs, S Kempin, I Silverberg, G Gonzales, MU Rarick, AM Myers, F Shepherd, C Sawka, MC Pike, ME Ross. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol 14:2353–2364, 1996.
8. TM Allen, C Hansen, J Rutledge. Liposomes with prolonged circulation times: factors affecting uptake by reticuloendothelial and other tissues. Biochim Biophys Acta 981:27–35, 1989.
9. D Papahadjopoulos, A Gabizon. Liposomes designed to avoid the reticuloendothelial system. Prog Clin Biol Res 343:85–93, 1990.
10. A Gabizon, D Papahadjopoulos. Liposome formulations with prolonged circulation time in blood and enhanced uptake by tumors. Proc Natl Acad Sci USA 85:6949–6953, 1988.
11. DD Lasic, FJ Martin, A Gabizon, SK Huang, D Papahadjopoulos. Sterically stabilized liposomes: a hypothesis on the molecular origin of the extended circulation times. Biochim Biophys Acta 1070:187–192, 1991.
12. D Needham, TJ McIntosh, DD Lasic. Repulsive interactions and mechanical stability of polymer-grafted lipid membranes. Biochim Biophys Acta 1108:40–48, 1992.
13. TM Allen, C Hansen, F Martin, C Redemann, A Yau-Young. Liposomes containing synthetic lipid derivatives of poly(ethylene glycol) show prolonged circulation half-lives in vivo. Biochim Biophys Acta 1066:29–36, 1991.

Copyright © 2003 Marcel Dekker, Inc.

14. AK Kenworthy, K Hristova, D Needham, TJ McIntosh. Range and magnitude of the steric pressure between bilayers containing phospholipids with covalently attached poly(ethylene glycol). Biophys J 68:1921–1936, 1995.
15. XP Hou, JM Zhang, XD Lu. [Effect of membrane modification by PEG on prolongation of circulation time of liposomes in blood in vivo]. Yao Hsueh Hsueh Pao 31: 451–454, 1996.
16. MC Woodle, DD Lasic. Sterically stabilized liposomes. Biochim Biophys Acta 1113:171–199, 1992.
17. MC Woodle, KK Matthay, MS Newman, JE Hidayat, LR Collins, C Redemann, FJ Martin, D Papahadjopoulos. Versatility in lipid compositions showing prolonged circulation with sterically stabilized liposomes. Biochim Biophys Acta 1105:193–200, 1992.
18. S Zalipsky, CB Hansen, JM Oaks, TM Allen. Evaluation of blood clearance rates and biodistribution of poly(2-oxazoline)-grafted liposomes. J Pharm Sci 85:133–137, 1996.
19. VP Torchilin. Polymer-coated long-circulating microparticulate pharmaceuticals. J Microencapsul 15:1–19, 1998.
20. VP Torchilin, VS Trubetskoy, KR Whiteman, P Caliceti, P Ferruti, FM Veronese. New synthetic amphiphilic polymers for steric protection of liposomes in vivo. J Pharm Sci 84:1049–1053, 1995.
21. VP Torchilin, MI Shtilman, VS Trubetskoy, K Whiteman, AM Milstein. Amphiphilic vinyl polymers effectively prolong liposome circulation time in vivo. Biochim Biophys Acta 1195:181–184, 1994.
22. MC Blok, EC van der Neut-Kok, LL van Deenen, J de Gier. The effect of chain length and lipid phase transitions on the selective permeability properties of liposomes. Biochim Biophys Acta 406:187–196, 1975.
23. S Clerc, Y Barenholz. Loading of amphipathic weak acids into liposomes in response to transmembrane calcium acetate gradients. Biochim Biophys Acta 1240:257–265, 1995.
24. AA Gabizon, R Catane, B Uziely, B Kaufman, T Safra, R Cohen, F Martin, A Huang, Y Barenholz. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. Cancer Res 54:987–992, 1994.
25. AA Gabizon, Y Barenholz, M Bialer. Prolongation of the circulation time of doxorubicin encapsulated in liposomes containing a polyethylene glycol-derivatized phospholipid: pharmacokinetic studies in rodents and dogs. Pharm Res 10:703–708, 1993.
26. Y Gazit, JW Baish, N Safabakhsh, M Leunig, LT Baxter, RK Jain. Fractal characteristics of tumor vascular architecture during tumor growth and regression. Microcirculation 4:395–402, 1997.
27. F Yuan, M Leunig, S Huang, DA Berk, D Papahadjopoulos, RK Jain. Distinct leaky patterns of Stealth liposomes in tumor versus normal vessels. Proc Am Assoc Cancer Res 1994 (abstract 2487).
28. F Yuan, M Leunig, S Huang, DA Berk, D Papahadjopoulos, RK Jain. Microvascular permeability and interstitial penetration of sterically stabilized (Stealth) liposomes in a human tumor xenograft. Cancer Res 54:3352–3356, 1994.

Copyright © 2003 Marcel Dekker, Inc.

29. SK Hobbs, WL Monsky, F Yuan, WG Roberts, L Griffith, VP Torchilin, RK Jain. Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. Proc Natl Acad Sci USA 95:4607–4612, 1998.
30. F Yuan, M Dellian, D Fukumura, M Leunig, DA Berk, VP Torchilin, RK Jain. Vascular permeability in a human tumor xenograft: molecular size dependence and cutoff size. Cancer Res 55:3752–3756, 1995.
31. SK Huang, FJ Martin, G Jay, J Vogel, D Papahadjopoulos, DS Friend. Extravasation and transcytosis of liposomes in Kaposi's sarcoma-like dermal lesions of transgenic mice bearing the HIV tat gene. Am J Pathol 143:10–14, 1993.
32. SK Huang, KD Lee, K Hong, DS Friend, D Papahadjopoulos. Microscopic localization of sterically stabilized liposomes in colon carcinoma-bearing mice. Cancer Res 52:5135–5143, 1992.
33. SK Huang, E Mayhew, S Gilani, DD Lasic, FJ Martin, D Papahadjopoulos, Pharmacokinetics and therapeutics of sterically stabilized liposomes in mice bearing C-26 colon carcinoma. Cancer Res 52:6774–6781, 1992.
34. FJ Martin. Clinical pharmacology and antitumor efficacy of DOXIL (pegylated liposomal doxorubicin). In: DD Lasic, D Papahadjopoulos, eds. Medical Applications of Liposomes. Amsterdam: Elsevier, 1998, pp. 635–688.
35. RM Schiffelers, IA Bakker-Woudenberg, SV Snijders, G Storm. Localization of sterically stabilized liposomes in *Klebsiella pneumoniae*–infected rat lung tissue: influence of liposome characteristics. Biochim Biophys Acta 1421:329–339, 1999.
36. IA Bakker-Woudenberg, MT ten Kate, LE Stearne-Cullen, MC Woodle. Efficacy of gentamicin or ceftazidime entrapped in liposomes with prolonged blood circulation and enhanced localization in *Klebsiella pneumoniae*–infected lung tissue. J Infect Dis 171:938–947, 1995.
37. AC Leenders, S de Marie, MT ten Kate, IA Bakker-Woudenberg, HA Verbrugh. Liposomal amphotericin B (AmBisome) reduces dissemination of infection as compared with amphotericin B deoxycholate (Fungizone) in a rate model of pulmonary aspergillosis. J Antimicrob Chemother 38:215–225, 1996.
38. IA Bakker-Woudenberg, AF Lokerse, MT ten Kate, JW Mouton, MC Woodle, G Storm. Liposomes with prolonged blood circulation and selective localization in *Klebsiella pneumoniae*–infected lung tissue. J Infect Dis 168:164–171, 1993.
39. RM Schiffelers, IA Bakker-Woudenberg, G Storm. Localization of sterically stabilized liposomes in experimental rat *Klebsiella pneumoniae* pneumonia: dependence on circulation kinetics and presence of poly(ethylene)glycol coating. Biochim Biophys Acta 1468:253–261, 2000.
40. ET Dams, WJ Oyen, OC Boerman, G Storm, P Laverman, PJ Kok, WC Buijs, H Bakker, JW van der Meer, FH Corstens. 99mTc-PEG liposomes for the scintigraphic detection of infection and inflammation: clinical evaluation. J Nucl Med 41:622–630, 2000.
41. P Laverman, S Zalipsky, WJ Oyen, ET Dams, G Storm, N Mullah, FH Corstens, OC Boerman. Improved imaging of infections by avidin-induced clearance of 99mTc-biotin-PEG liposomes. J Nucl Med 41:912–918, 2000.
42. P Laverman, OC Boerman, WJ Oyen, ET Dams, G Storm, FH Corstens. Liposomes for scintigraphic detection of infection and inflammation. Adv Drug Del Rev 37: 225–235, 1999.

Copyright © 2003 Marcel Dekker, Inc.

43. E Mayhew, R Lazo, WJ Vail, J King, AM Green. Characterization of liposomes prepared using a microemulsifier. Biochim Biophys Acta 775:169–174, 1984.
44. F Olson, CA Hunt, FC Szoka, WJ Vail, D Papahadjopoulos. Preparation of liposoms of defined size distribution by extrusion through polycarbonate membranes. Biochim Biophys Acta 557:9–23, 1979.
45. D Papahadjopoulos, TM Allen, A Gabizon, E Mayhew, K Matthay, SK Huang, KD Lee, MC Woodle, DD Lasic, C Redemann. Sterically stabilized liposomes: improvements in pharmacokinetics and antitumor therapeutic efficacy. Proc Natl Acad Sci USA. 88:11460–11464, 1991.
46. SK Huang, E Mayhew, S Gilani, DD Lasic, FJ Martin, D Papahadjopoulos. Pharmacokinetics and therapeutics of sterically stabilized liposomes in mice bearing C-26 colon carcinoma. Cancer Res 52:6774–6781, 1992.
47. J Vaage, E Barbera-Guillem, R Abra, A Huang, P Working. Tissue distribution and therapeutic effect of intravenous free or encapsulated liposomal doxorubicin on human prostate carcinoma xenografts. Cancer 73:1478–1484, 1994.
48. J Vaage, D Donovan, E Mayhew, R Abra, A Huang. Therapy of human ovarian carcinoma xenografts using doxorubicin encapsulated in sterically stabilized liposomes. Cancer 72:3671–3675, 1993.
49. SS Williams, TR Alosco, E Mayhew, DD Lasic, FJ Martin, RB Bankert. Arrest of human lung tumor xenograft growth in severe combined immunodeficient mice using doxorubicin encapsulated in sterically stabilized liposomes. Cancer Res 53: 3964–3967, 1993.
50. A Gabizon, R Catane, B Uziely, B Kaufman, T Safra, R Cohen, F Martin, A Huang, Y Barenholz. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. Cancer Res 54:987–992, 1994.
51. DW Northfelt, FJ Martin, P Working, PA Volberding, J Russell, M Newman, MA Amantea, LD Kaplan. Doxorubicin encapsulated in liposomes containing surface-bound polyethylene glycol: pharmacokinetics, tumor localization, and safety in patients with AIDS-related Kaposi's sarcoma. J Clin Pharmacol 36:55–63, 1996.
52. KJ Harrington, CS Gooden, S Mohammedtaghi, AA Epenetos, JS Stewart. Biodistribution and pharmacokinetics of ^{111}In labeled Stealth liposomes in patients with solid tumors. Proc Am Soc Clin Oncol, 1996 (abstract 1511).
53. SS Stewart, KJ Harrington. The biodistribution and pharmacokinetics of Stealth liposomes in patients with solid tumors. Oncology 11(suppl 11):33–37, 1997.
54. DW Northfelt, BJ Dezube, JA Thommes, BJ Miller, MA Fischl, A Friedman-Kien, LD Kaplan, C Du Mond, RD Mamelok, DH Henry. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol 16: 2445–2451, 1998.
55. S Stewart, H Jablonowski, FD Goebel, K Arasteh, M Spittle, A Rios, D Aboulafia, J Galleshaw, BJ Dezube. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol 16:683–691, 1998.

Copyright © 2003 Marcel Dekker, Inc.

56. DW Northfelt. Liposomal anthracycline chemotherapy in the treatment of AIDS-related Kaposi's sarcoma. Oncology 11(suppl 11):21–32, 1997.
57. DW Northfelt, BJ Dezube, JA Thommes, R Levine, JH Von Roenn, GM Dosik, A Rios, SE Krown, C DuMond, RD Mamelok. Efficacy of pegylated-liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma after failure of standard chemotherapy. J Clin Oncol 15:653–659, 1997.
58. FD Goebel, D Goldstein, M Goos, H Jablonowski, JS Stewart. Efficacy and safety of Stealth liposomal doxorubicin in AIDS-related Kaposi's sarcoma. The International SL-DOX Study Group. Br J Cancer 73:989–994, 1996.
59. FD Goebel, M Gruenaug, JR Bogner. Survival times of patients with AIDS-related Kaposi's sarcoma with pulmonary involvement using liposomal doxorubicin. Proc Am Soc Clin Oncol, 1996 (abstract 860).
60. M Harrison, D Tomlinson, S Stewart. Liposomal-entrapped doxorubicin: an active agent in AIDS-related Kaposi's sarcoma. J Clin Oncol 13:914–920, 1995.
61. F Muggia, J Blessing, J Sorosky, G Reid. Phase II study of pegylated liposomal doxorubicin (DOXIL) in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study (GOG #129-H). Proc Am Soc Clin Oncol, 2000 (abstract 151).
62. FM Muggia, JD Hainsworth, S Jeffers, P Miller, S Groshen, M Tan, L Roman, B Uziely, L Muderspach, A Garcia, A Burnett, FA Greco, CP Morrow, LJ Paradiso, LJ Liang. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. J Clin Oncol 15:987–993, 1997.
63. F Muggia, J Hainsworth, S Jeffers, S Groshen, M Tan. Liposomal doxorubicin (DOXIL) is active against refractory ovarian cancer. Proc Am Soc Clin Oncol, 1996 (abstract 781).
64. AN Gordon, CO Granai, PG Rose, J Hainsworth, A Lopez, C Weissman, R Rosales, T Sharpington. Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. J Clin Oncol 18:3093–3100, 2000.
65. A Gordon, J Fleagl, D Guthrie, DE Parkin, M Gore, AJ Lacave, D Mutch. Interim analysis of a phase III randomized trial of Doxil/Caelyx (D) versus topotecan (T) in the treatment of patients with relapsed ovarian cancer). Proc Am Soc Clin Oncol, 2000 (abstract 1504).
66. MR Ranson, J Carmichael, K O'Byrne, S Stewart, D Smith, A Howell. Treatment of advanced breast cancer with sterically stabilized liposomal doxorubicin: results of a multicenter phase II trial. J Clin Oncol 15:3185–3191, 1997.
67. JW Park, K Hong, DB Kirpotin, O Meyer, D Papahadjopoulos, CC Benz. Anti-HER2 immunoliposomes for targeted therapy of human tumors. Cancer Lett 118: 153–160, 1997.
68. D Kirpotin, JW Park, K Hong, S Zalipsky, WL Li, P Carter, CC Benz, D Papahadjopoulos. Sterically stabilized anti-HER2 immunoliposomes: design and targeting to human breast cancer cells in vitro. Biochemistry 36:66–75, 1997.
69. JW Park, K Hong, DB Kirpotin, D Papahadjopoulos, CC Benz. Immunoliposomes for cancer treatment. Adv Pharmacol 40:399–435, 1997.
70. D Goren, AT Horowitz, D Tzemach, M Tarshish, S Zalipsky, A Gabizon. Nuclear

Copyright © 2003 Marcel Dekker, Inc.

delivery of doxorubicin via folate-targeted liposomes with bypass of multidrug-resistance efflux pump. Clin Cancer Res 6:1949–1957, 2000.
71. T Murohara, J Margiotta, LM Phillips, JC Paulson, S DeFrees, S Zalipsky, LS Guo, AM Lefer. Cardioprotection by liposome-conjugated sialyl Lewis^{x}-oligosaccharide in myocardial ischaemia and reperfusion injury. Cardiovasc Res 30:965–974, 1995.
72. S Zalipsky, M Qazen, JA Walker, 2nd, N Mullah, YP Quinn, SK Huang. New detachable poly(ethylene glycol) conjugates: cysteine-cleavable lipopolymers regenerating natural phospholipid, diacyl phosphatidylethanolamine. Bioconjug Chem 10: 703–707, 1999.
73. S Druckmann, A Gabizon, Y Barenholz. Separation of liposome-associated doxorubicin from non-liposome-associated doxorubicin in human plasma: implications for pharmacokinetic studies. Biochim Biophys Acta 980:381–384, 1989.

Copyright © 2003 Marcel Dekker, Inc.

59
DepoFoam Technology

Sankaram Mantripragada
SkyePharma Inc., San Diego, California, U.S.A.

I. INTRODUCTION

DepoFoam® technology is a proprietary, lipid-based drug delivery system that can be used to encapsulate a wide variety of drugs, including small molecules, proteins, peptides, and nucleic acids. SkyePharma is developing products to satisfy medical needs in cancer, pain management, and other fields. DepoFoam technology can be used with approved or late-stage pharmaceuticals to create new therapeutic products that may offer clinical, economic, and commercial benefits.

The DepoFoam system is protected by over 100 issued or pending patents in the United States, Europe, and Asia. These patents cover the technology, manufacturing process, and specific formulations. A representative list of patents is provided in Table 1. Safety of DepoFoam formulations has been demonstrated in preclinical and clinical studies, and regulatory agencies in the United States, Canada, Europe, and Japan are familiar with the DepoFoam technology. The first sustained-release injectable product based on the DepoFoam technology is a cancer drug, DepoCyt®, which was approved for marketing by the U.S. Food and Drug Administration, Health Canada, and the European Agency for the Evaluation of Medicinal Products. The second sustained-release injectable product being developed is for pain management: DepoMorphine™, which is currently in phase III clinical trials. An antibiotic formulation (DepoAmikacin) has been through Phase I clinical trials in the United States. A number of additional formulations for small molecules, peptides, proteins, antisense oligonucleotides, DNA vaccines, and plasmids for gene therapy are in various states of preclinical development.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Representative List of Published Patents

World Intellectual Property Organization (WIPO) publication no.	Title
91/14445	Heterovesicular liposomes
94/23697	Cyclodextrin liposomes encapsulating pharmacological compounds and methods for their use
94/26250	Method for treating neurological disorders
95/13796	Vesicles with controlled release of actives
96/08235	Preparation of multivesicular liposomes for controlled release of active agents
97/03652	Epidural administration of therapeutic compounds with sustained rate of release
98/14171	Method for producing liposomes with increased percentage of compound encapsulated
98/33483	Method for utilizing neutral lipids to modify in vivo release from multivesicular liposomes
99/12522	High and low load formulations of IGF-1 in multivesicular liposomes
99/12523	Modulation of drug loading in multivesicular liposomes
99/13865	Sustained-release liposomal anesthetic compositions

II. DEPOFOAM TECHNOLOGY

DepoFoam particles include hundreds of bilayer-enclosed, aqueous compartments [1–3]. They are formed by first emulsifying a mixture of an aqueous phase containing the compounds to be encapsulated and an organic phase containing lipids. The first emulsion is then dispersed and emulsified in a second aqueous phase. After the organic solvent is evaporated, numerous submicrometer- to micrometer-sized water compartments are separated by lipid bilayers and take on a close-packed polyhedral structure [4–8]. The compartments in the DepoFoam particle efficiently entrap a variety of compounds that then slowly permeate through the bilayers (Fig. 1).

DepoFoam particles have a unique multivesicular structure. Sustained release is achieved without a burst effect, since all active drug is encapsulated within the multiple chambers of individual particles [9]. The duration of release can be tailored according to the desired therapeutic regimen by changing manufacturing parameters and the composition of DepoFoam particles [10–15]. SkyePharma has created formulations that deliver drugs for periods as short as 1 day and as long as several weeks. Because less than 5% by weight of DepoFoam is

Copyright © 2003 Marcel Dekker, Inc.

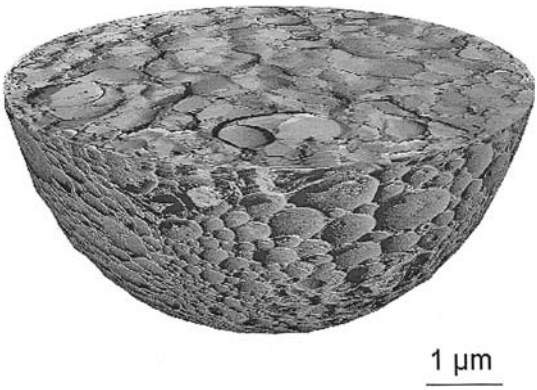


Figure 1 Composite electron micrograph of freeze-fracture replicas of a DepoFoam particle [2].

the lipid structure, large amounts of drug can be loaded in solution within the particles. The result is a ready-to-use injectable suspension.

Drugs that require delivery via the injectable route often have molecular-size complexity or vulnerability to the stomach that prevents them from administration via the oral route. Innovations in biotechnology have led to an increase in the number of large-molecule protein and peptide drugs under development. Many of these potentially important products cannot be commercialized owing to their short duration of action or require multiple injections. By incorporating these molecules in DepoFoam particles a release profile can be achieved ranging from a few hours to 45 days [16,17].

DepoFoam formulations can be delivered into the body by a number of routes including under the skin, within the muscle tissue, into the spinal fluid, within joints, and within the abdominal cavity (Fig. 2). Because the components of DepoFoam (phospholipids, cholesterol, triglycerides) are synthetic duplicates of lipids normally present in the body, the material is biodegradable and biocompatible. DepoFoam formulations address many of the limitations associated with traditional methods of delivering drugs.

III. DEPOFOAM APPLICATIONS

Potential clinical uses for DepoFoam formulations of a number of different drugs are under investigation, including antineoplastic agents, anesthetics, analgesics, antibiotics, antivirals, cytokines, growth factors, peptide hormones, DNA vaccines, and plasmids.

Copyright © 2003 Marcel Dekker, Inc.

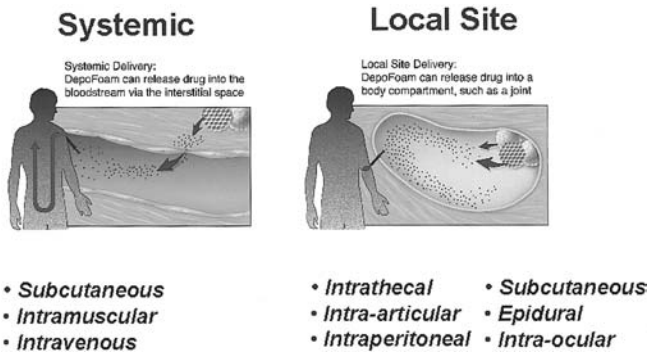


Figure 2 Local and systemic routes of administration for DepoFoam formulations. (See color insert.)

A. Cancer

Initial studies with DepoFoam formulations were focused on obtaining sustained release of cancer chemotherapeutic agents, particularly those whose potency increases with increasing duration of exposure, such as cytarabine (cytosine arabinoside), methotrexate, and bleomycin. A summary of the pharmacokinetic advantage conferred by DepoFoam encapsulation for antineoplastic drugs is provided in Table 2. For example, in the initial phase I/II trial of DepoCyt, elimination of cytarabine from the cerebrospinal fluid after intrathecal administration was biexponential, with a mean half-life of 9.4 h for the initial phase and 141 h for the terminal phase [18,19]. This was a significant improvement over the half-life of 3.4 h for unencapsulated cytarabine.

B. Anesthetics and Analgesics

After subcutaneous administration to mice of 1.0 mg of DepoFoam-encapsulated morphine sulfate (DepoMorphine), serum morphine concentration peaked at 1.21 μg/mL 1 h after injection and then decreased with a half-life of 8.33 days, compared to only 0.45 h for unencapsulated morphine [20]. Epidural administration of DepoMorphine or bupivacaine has also been associated with significant prolongation of analgesia in animals [21,22]. Evaluation of hemoglobin oxygen saturation, animal behavior, and corneal reflexes showed no adverse effects associated with the epidural administration of DepoMorphine [21].

DepoMorphine is intended for use to relieve postoperative pain in many types of surgery, including deep abdominal surgeries, hip and knee replacements, hysterectomies, cesarean sections, and other surgical procedures involving pain that can be blocked by epidural administration. By offering a simple, single-

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Pharmacokinetics of DepoFoam-Encapsulated Versus Unencapsulated Antineoplastic Drugs [19]

Antineoplastic drug	Model	Route of administration	Terminal half-life	
			Unencapsulated	DepoFoam-encapsulated
Cytarabine	BDF_1 mice	Intraperitoneal	16 min	165 h
Cytarabine	BDF_1 mice	Intralesional	12 min	26 h
Cytarabine	BDF_1 mice	Subcutaneous	10 min	96 h
Cytarabine	Sprague-Dawley rats	Intraventricular	2.7 h	148 h
Cytarabine	Rhesus monkeys	Intralumbar	0.74 h	156 h
Cytarabine	NM patients	Intraventricular	3.4 h	140 h
Cytarabine	NM patients	Intraventricular	3.4 h	141 h
Methotrexate	Sprague-Dawley rats	Intracisternal	7.2 h	129.6 h
Methotrexate	BDF_1 mice	Intraperitoneal	0.5 h	39.6 h
Methotrexate	BDF_1 mice	Subcutaneous	0.16 h	49.7 h
Bleomycin	BDF_1 mice	Subcutaneous	8 min	31.8 h

NM, Neoplastic Meningitis.

injection approach to postsurgical pain management, sustained-release DepoMorphine may provide a range of advantages, including elimination of multiple injections, elimination of an indwelling epidural catheter, continuous pain relief, improved safety, greater convenience for patient and physician, and faster patient recovery from surgery.

C. Antibiotics and Antivirals

Antibiotics are essential medical tools for treating patients with bacterial infections. However, administration of these drugs orally, by bolus injection or by continuous infusion, to treat site-specific or localized infections is problematic. Conventional delivery methods provide high systemic concentrations of drug, but low local concentrations in the infected tissue. In addition, drugs administered in conventional doses are generally eliminated from the body within several hours. In the case of amikacin, the amount of drug that can be given systemically is further limited by potential toxicities to the kidneys and auditory nerves. Because DepoAmikacin provides sustained concentrations of drug at the site of a local infection, it is possible that this approach will result in a variety of clinical applications in the treatment and prophylaxis of bacterial infections during high-risk surgeries, orthopedic implants, and indwelling vascular catheters that may

Copyright © 2003 Marcel Dekker, Inc.

qualify for site-specific antibiotic treatment [23,24]. DepoAmikacin may also find application in emergency room situations involving trauma.

Poor penetration of antiviral drugs across the blood-brain barrier after oral or intravascular administration renders treatment of viral infections in the central nervous system difficult. In animal studies, intrathecal delivery of DepoFoam formulations of an antiretroviral agent, 2′,3′-dideoxycytidine, have been used to inhibit replication of the human immunodeficiency virus. In these studies, a single intraventricular injection of 50 μg of the DepoFoam formulation maintained antiviral concentrations (0.1 μg/mL) for up to 68 h. The half-life for 2′,3′-dideoxycytidine in the cerebrospinal fluid was 23 h with the DepoFoam vehicle and only 1.1 h for the unencapsulated drug [25–27].

In a rabbit model of bacterial keratitis, a single subconjuctival injection of DepoFoam-encapsulated tobramycin produced reductions in corneal bacterial counts after 24 h that were similar to those obtained with frequent instillation of topical tobramycin. Thus, treatment of corneal infections is a potential indication for DepoFoam formulations. In another study in ophthalmology, an injection to rabbits of DepoFoam -encapsulated 2′-norcyclic guanosine monophosphate (a cyclophosphate derivative of ganciclovir) provided long-lasting protection against development of herpes simplex virus type 1 retinitis [28].

D. Macromolecules

Pharmacokinetic advantage of sustained-release injection by DepoFoam-encapsulation has been demonstrated for a number of macromolecules. These include interleukin-2, human insulin, enkephalin, octreotide, granulocyte-colony-stimulating factor, granulocyte-macrophage-colony-stimulating factor, leutenizing-hormone-releasing hormone, insulin-like growth factor 1, and interferon alpha. All of these peptides or proteins in the currently marketed form are administered by multiple injections daily or weekly. Preclinical studies reviewed elsewhere demonstrate that once-a-week to once-a-month injections are feasible with DepoFoam-encapsulation [17]. In a number of unpublished studies, antisense oligonucleotides and plasmids were encapsulated successfully and sustained gene expression demonstrated.

IV. CONCLUSION

A number of preclinical and clinical studies outlined in this chapter highlight the advantages of injectable sustained-release delivery with DepoFoam formulations. Unlike microsphere formulations that require reconstitution of lyophilized materials prior to injection, DepoFoam formulations in the vial are ready to use. Further, DepoFoam formulations are made up of phospholipids, cholesterol, and

Copyright © 2003 Marcel Dekker, Inc.

triglycerides as opposed to synthetic polymers such as polylactide, poly(lactide-glycolide), etc. Therefore, better biocompatibility of the DepoFoam delivery system is both expected and experimentally demonstrated because lipid degradation is a native physiological process, whereas presentation of the polymeric microspheres is expected to require triggering of a new physiological event. DepoFoam technology also offers significant advantages over other commercial lipid-based delivery systems (e.g., lipid complexes, lipid emulsions, liposomes with and without pegylated lipids). The unique close-packed multivesicular structure confers a longer duration of release since rupture of one of several hundred internal vesicles results in the release of only a small amount of drug, unlike a unilamellar vesicle the drug within which can be released by one scission in the lipid bilayer enclosing it. The micrometer range of DepoFoam particles allows for a higher loading than submicron-sized lipid-based products. As a result, therapeutically effective bioavailability is achieved by nonvascular single-bolus administration compared to intravenous infusion.

REFERENCES

1. S Kim, MS Turker, EY Chi, S Sela, GM Martin. Preparation of multivesicular liposomes. Biochim Biophys Acta 728:339–348, 1983.
2. MS Spector, JA Zasadzinski, MB Sankaram. Topology of multivesicular liposomes, a model biliquid foam. Langmuir 12:4704–4708, 1996.
3. JF Ellena, M Le, D Cafiso, RM Solis, M Langston, MB Sankaram. Distribution of phospholipids and triglycerides in multivesicular lipid particles. Drug Del 6:97–106, 1999.
4. C Pepper, M Patel, H Hartounian. cGMP Manufacturing scale-up of multivesicular lipid based drug delivery system. Pharm Eng 19:8–18, 1999.
5. C Pepper, M Patel, H Hartounian. CGMP pharmaceutical scale-up. Part 1. Design. BioPharm 12:26–34, 1999.
6. C Pepper, M Patel, H Hartounian. CGMP pharmaceutical scale-up. Part 2. Contractors and request for proposal. BioPharm 12:36–55, 1999.
7. C Pepper, M Patel, H Hartounian. CGMP pharmaceutical scale-up. Part 3. Automation. BioPharm 12:52–54, 1999.
8. C Pepper, M Patel, H Hartounian. CGMP pharmaceutical scale-up. Part 4. Installation, commissioning, development. BioPharm 13:28–34, 2000.
9. RRC New. Influence of liposome characteristics on their properties and fate. In: JR Philippot, F Schuber, eds. Liposomes as Tools in Basic Research and Industry. Boca Raton, FL: CRC Press, 1995, pp. 3–20.
10. S Kim. Cyclodextrin liposomes encapsulating pharmacologic compounds and methods for their use. US patent 5,759,573, 1998.
11. MB Sankaram, S Kim. Multivesicular liposomes with controlled release of encapsulated biologically active substances. US patent 5,766,627, 1998.

Copyright © 2003 Marcel Dekker, Inc.

12. RC Willis. Method for utilizing neutral lipids to modify in vivo release from multivesicular liposomes. US patent 5,891,467, 1999.
13. MB Sankaram, S Kim. Preparation of multivesicular liposomes for controlled release of encapsulated biologically active substances. US patent 5,993,850, 1999.
14. Q Ye, MB Sankaram. Method for producing liposomes with increased percent of compound encapsulated. US patent 5,997,899, 1999.
15. Q Ye, N Katre, MB Sankaram. Modulation of drug loading in multivesicular liposomes. US patent 6,106,858, 2000.
16. S Mantripragada. DepoFoam technology for sustained release injectable drug delivery. Drug Del Syst Sci 1:13–16, 2001.
17. Q Ye, J Asherman, M Stevenson, E Brownson, NV Katre. DepoFoam technology: a vehicle for controlled delivery of protein and peptide drugs. J Control Rel 64:155–166, 2000.
18. MC Chamberlain, S Khatibi, JC Kim, SB Howell, E Chatelut, S Kim. Treatment of leptomeningeal metastasis with intraventricular administration of depot cytarabine (DTC 101): a phase I study. Arch Neurol 50:261–264, 1993.
19. SB Howell. Clinical applications of a novel sustained-release injectable drug delivery system: DepoFoam technology. Cancer J 7:219–227, 2001.
20. T Kim, J Kim, S Kim. Extended-release formulation of morphine for subcutaneous administration. Cancer Chemother Pharmacol 33:187–190, 1993.
21. T Kim, S Murdande, A Gruber, S Kim. Sustained-release morphine for epidural analgesia in rats. Anesthesiology 85:331–338, 1996.
22. S Murdande, T Kim, A Gruber, S Kim. DepoBupivacaine for prolonged epidural analgesia. XV Annual ESRA Congress, Nice, France, 1996 (abstract).
23. J Huh, JC Chen, GM Furman, C Malki, B King, F Kafie, SE Wilson. Local treatment of prosthetic vascular graft infection with multivesicular liposome-encapsulated amikacin. J Surg Res 74:54–58, 1998.
24. AA Roehrborn, JF Hansbrough, B Gualdoni, S Kim. Lipid-based slow-release formulation of amikacin sulfate reduces foreign body-associated infections in mice. Antimicrob Agents Chemother 39:1752–1755, 1995.
25. S Shakiba, KK Assil, AD Listhaus, D Munguia, M Flores-Aguilar, C Vuong, CA Wiley, RL Tolman, JD Karkas, G Bergeron-Lynn. Evaluation of retinal toxicity and liposome encapsulation of the anti-CMV drug 2′-nor-cyclic GMP. Invest Ophthalmol Vis Sci 34:2903–2910, 1993.
26. G Besen, M Flores-Aguilar, KK Assil, BD Kupperman, P Gangan, M Pursley, D Munguia, C Vuong, E De Clercq, G Bergeron-Lynn. Long-term therapy for herpes retinitis in an animal model with high-concentrated liposome-encapsulated HPMPC. Arch Ophthalmol 113:661–668, 1995.
27. BD Kuppermann, KK Assil, C Vuong, G Besen, CA Wiley, E De Clercq, G Bergeron-Lynn, JD Connor, M Pursley, D Munguia, WR Freeman. Liposome-encapsulated (S)-1-(3-hydroxy-2- phosphonylmethoxypropyl)cytosine for long-acting therapy of viral retinitis. J Infect Dis 173:18–23, 1996.
28. KK Assil, J Frucht-Perry, E Ziegler, DJ Schanzlin, T Schneiderman, RN Weinreb. Tobramycin liposomes. Single subconjunctival therapy of pseudomonal keratitis. Invest Ophthalmol Vis Sci 32:3216–3220, 1991.

Copyright © 2003 Marcel Dekker, Inc.

60

Medipad Delivery System: Controlled Macromolecule Delivery

Izrail Tsals and Diana Davidson
Elan Drug Delivery, King of Prussia, Pennsylvania, U.S.A.

I. INTRODUCTION

The extensive growth in the development of therapeutic biotechnology products for the treatment of a wide range of conditions has challenged the pharmaceutical industry to develop patient-friendly drug delivery systems for these compounds [1]. Noninvasive delivery systems such as pulmonary, oral, and buccal are in development but today, marketed protein and macromolecule compounds are predominantly delivered by intravenous, intramuscular, or subcutaneous (SC) administration. Historically, the SC route is favored by patients and caregivers, since it permits self-administration [2]. This route also has the advantage of high bioavailability, which is critical for expensive biotechnology-derived substances. Standard syringes, prefilled syringes, pen injectors, or jet injectors are successfully used today by large patient populations for SC administration of compounds such as low-molecular-weight heparin, α-interferon, β-interferon, insulin, and growth hormone on an outpatient basis. The incidence of infection and complications by this route is low.

Such bolus systems, however, are inadequate when prolonged delivery of a compound is required, for example, compounds with a short half-life. Formulation-based depot or pegylation technologies are becoming increasingly popular, but the development of a depot-injectable formulation may take several years, delaying entrance to clinical development. Continuous delivery via ambulatory infusion pumps is available; however, these pumps are costly and require extensive patient education. The Medipad™ delivery system has been developed to

Copyright © 2003 Marcel Dekker, Inc.

address the limitations of current drug delivery systems for sustained delivery of peptides and macromolecules.

II. HISTORICAL DEVELOPMENT

With the advent of bioengineering of proteins and macromolecules, Elan investigated oral delivery of proteins and peptides as well as other delivery technology platforms that could provide noninvasive or minimally invasive delivery of proteins and macromolecules. One of the first technologies explored was drug delivery via the skin. Passive transdermal delivery is limited to a few compounds with low molecular weights. Peptides and proteins do not cross the skin unaided [2]. Application of a small electrical current (electrotransdermal or iontophoretic delivery programs) produced enhancement of transdermal peptide and protein delivery, but in many cases the delivery was less than required for therapeutic effectiveness and skin irritation was reported with repeated delivery of some compounds. Still utilizing administration through the skin, researchers then explored the idea of using a small mechanical probe to overcome the skin barrier coupled with a pumping mechanism. These concepts were incorporated into the Medipad Pump-In-A-Patch™ delivery system.

III. DESCRIPTION OF THE TECHNOLOGY

The Medipad system is a unique, non-formulation-specific drug delivery system designed for prolonged, controlled, SC delivery of small-volume medications. This disposable, single-use drug delivery system (Fig. 1) contains a microinfusor and integrated needle to deliver the drug subcutaneously. An adhesive backing allows the lightweight, pump-in-a-patch system to be worn on the skin, discreetly under clothing. The Medipad system offers an alternative to external ambulatory infusion pumps or controlled-release formulations for drug compounds that may be difficult to deliver via other means owing to poor oral bioavailability, short half-life, or a narrow therapeutic window.

The Medipad system utilizes precise, controlled electrochemical gas generation as the delivery mechanism. Major components of the MEDIPAD system include the top and bottom housings, the drug reservoir, SC needle, and gas generator, as shown in Figure 2.

Drug is placed into a small reservoir in the Medipad system bounded by an elastomeric membrane and a hard plastic housing. When the “Start” area on the top of the Medipad system is pressed, the top housing moves downward, causing the needle to penetrate the skin and starting the current flow. Small amounts of harmless gas are generated when current is applied to the electrolytic

Copyright © 2003 Marcel Dekker, Inc.

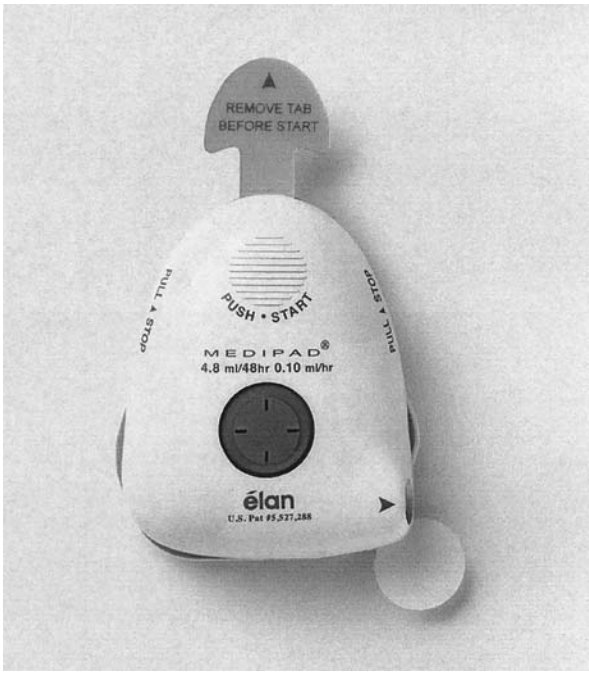


Figure 1 The Medipad delivery system.

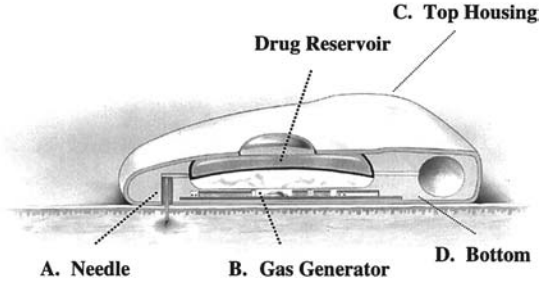


Figure 2 Side view of the Medipad system with major components. In this schematic, the system has been started and has delivered over half the contents of the drug reservoir. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

cell. The gas presses on the elastomeric membrane causing fluid to be expelled via the needle into the SC tissue. Unlike many infusion pumps, which achieve "continuous" delivery via a series of small pulses, the Medipad system continuously infuses drug throughout the prescribed use time.

A Medipad system is approximately 85 mm × 62 mm × 20 mm, and an empty system without filling adapters weighs less than 50 g. Delivery volume, rate, and use time are preset during manufacturing and are mated to specific requirements needed for a particular compound. No adjustments can be made by the user. The system is capable of delivery rates as low as 0.060 mL/h and as high as 2 mL/h with nominal delivery times of 2 h, 10 h, 48 h, and 72 h [3].

The Medipad system is designed for self-administration by a patient or caregiver in an outpatient or home setting, thereby helping to minimize health care costs. For commercialization, a Medipad system would be packaged along with a unit dose of drug as a drug/device combination to simplify dispensing. The system is supplied sterile and is filled with drug by the patient or caregiver just prior to use. Filling is accomplished via a standard syringe or a custom drug cartridge. Matched to the Medipad system volume, the drug cartridge system simplifies drug filling and minimizes contamination potential. Figures 3a–3f illustrate the main steps for filling and applying a Medipad system with the cartridge adapter.

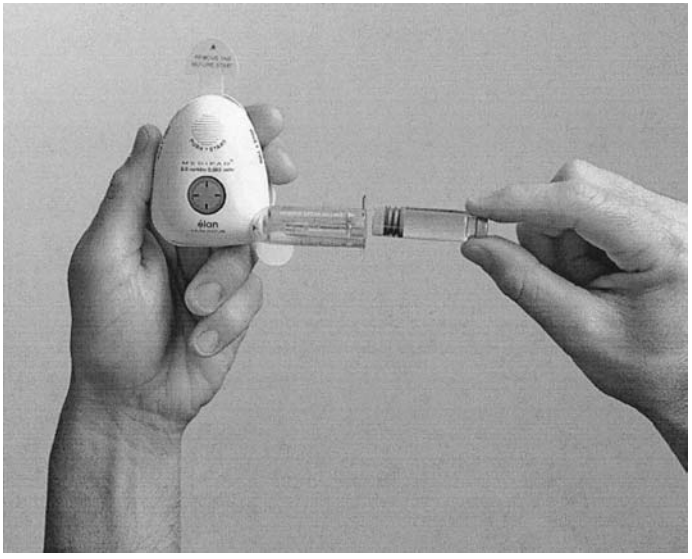


Figure 3a Insertion of the custom drug cartridge into the Medipad system cartridge adapter.

Copyright © 2003 Marcel Dekker, Inc.

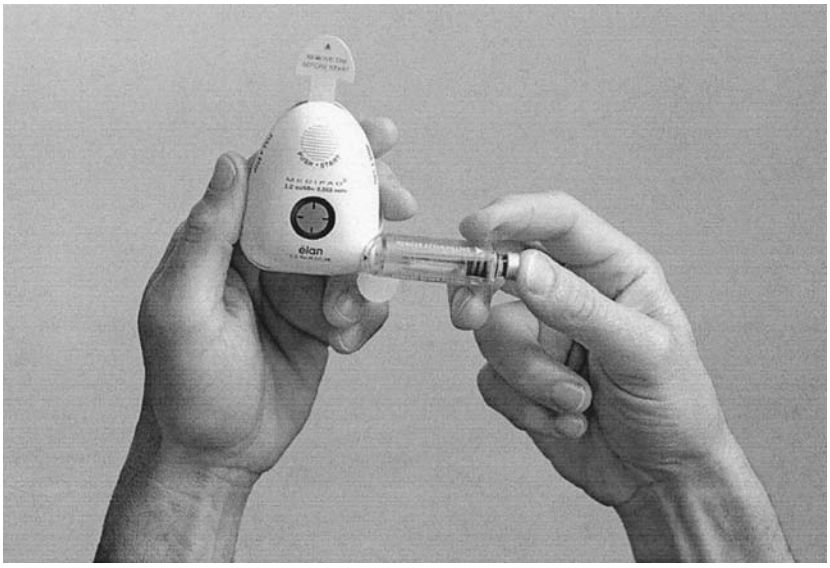


Figure 3b The drug cartridge is fully inserted into the Medipad cartridge adapter. This action transfers drug from the cartridge into the Medipad reservoir.

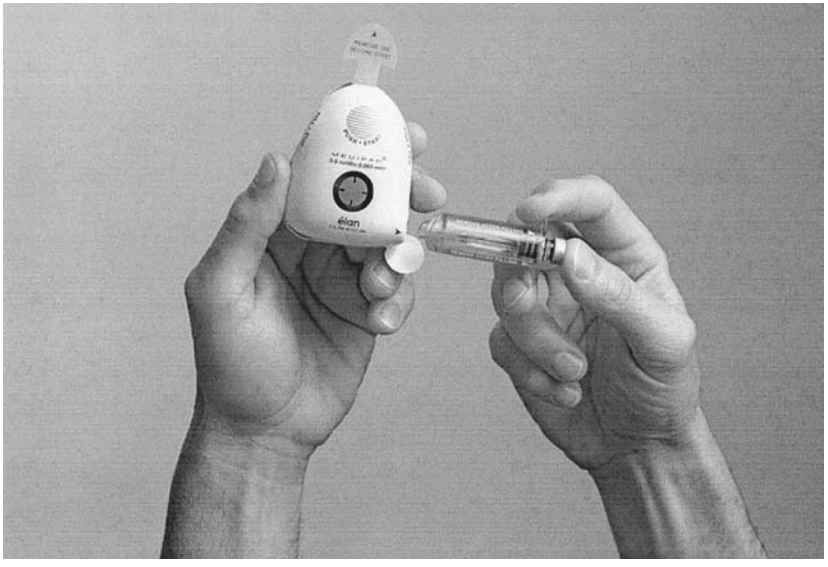


Figure 3c The drug cartridge and transfer system are removed.

Copyright © 2003 Marcel Dekker, Inc.

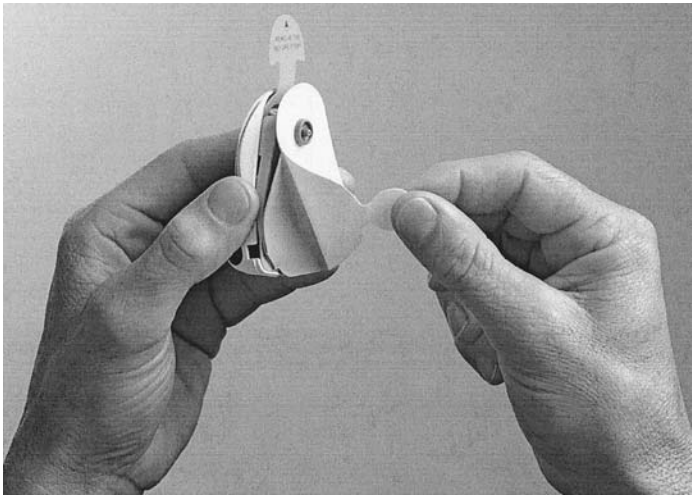


Figure 3d The protective liner is removed exposing the adhesive backing.

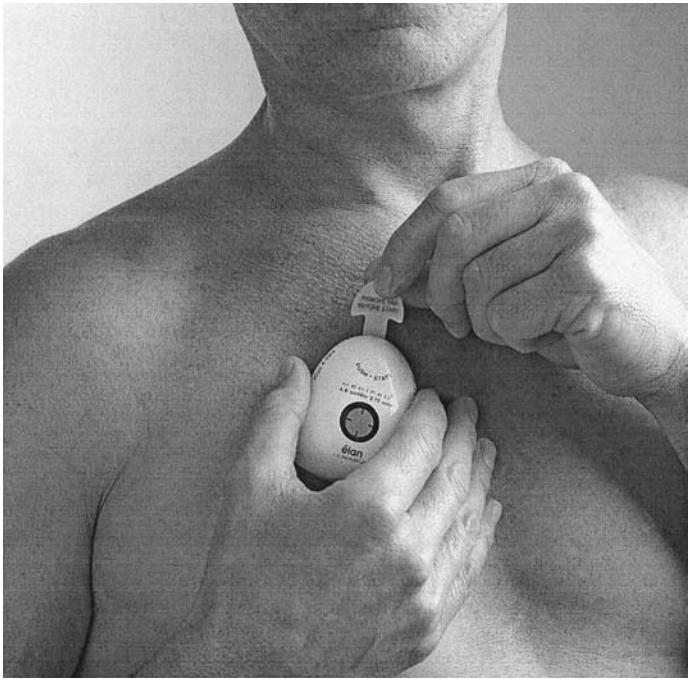


Figure 3e The Medipad system is placed at an application site and the safety tab is removed.

Copyright © 2003 Marcel Dekker, Inc.

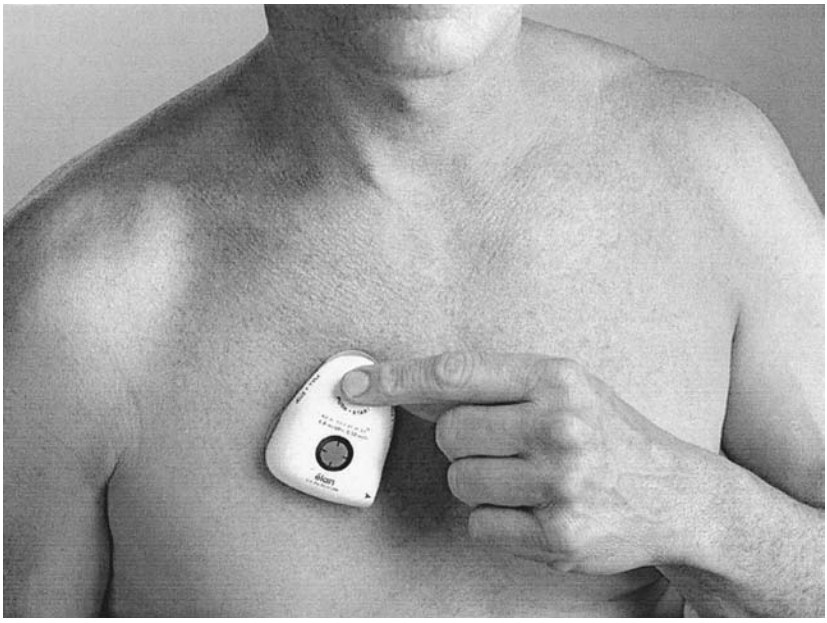


Figure 3f The start area is pressed on the system initiating drug delivery.

The Medipad system features a unique three-position needle mechanism that facilitates proper needle insertion into the SC tissue at the correct depth and angle. Prior to application, the needle is retained in the top housing and is not visible. When used as directed, the needle should not be visible to the user throughout application and removal, thus minimizing needle phobia.

A patient can maintain virtually all activities of daily living while wearing the device. The Medipad system is water-resistant (splash-proof) and patients can shower while wearing the device. The device, however, is not waterproof and should not be immersed. The system is contraindicated for patients with known allergies to adhesive bandages or patients who do not have the cognitive abilities to use the Medipad according to instructions.

IV. RESEARCH AND DEVELOPMENT

A detailed functional requirement specification was generated for the Medipad system based on customer requirements as well as Food and Drug Administration (FDA) and European standards for external infusion pumps. Early Medipad pro-

Copyright © 2003 Marcel Dekker, Inc.

totype systems were hand-assembled and employed machined, plastic components. The resultant systems were initially used in various in vitro tests to achieve delivery within specification over a particular time. Preclinical in vivo experiments performed in rabbits and pigs demonstrated successful delivery of a range of proteins and peptides including insulin and salmon calcitonin, as well as small molecules such as sumatriptan [4]. On the basis of successful delivery in these studies, a number of phase I studies were performed in human volunteers to study the continuous infusion of compounds over a longer use time [1]. Compounds selected for these assessments included morphine and sumatriptan as well as saline.

The development of Medipad required resolution of a number of technical issues, one of which was the minimization of back pressures generated during continuous SC microinfusion. At the time of development, minimal information existed in the literature on the physiology of back pressures encountered during SC infusion. High pressure encountered in the SC tissue was circumvented by using a 5-mm, 26-gauge, multiorifice needle. Numerous needle geometries were tested, and the design of the final multiorifice needle was optimized during several preclinical studies in pigs, as the pig model represents the closest model to human SC tissue. The multiorifice needle was confirmed in Medipad system studies infusing saline in healthy volunteers, as well as a phase I pharmacokinetic study. This needle was then incorporated into the Medipad system design [5].

Another development task necessary for a gas-actuated delivery system was a complete thermal evaluation of system operating conditions. An in vivo thermal evaluation was initially performed on human volunteers, followed by an extensive in vitro simulation where wider temperature variations could be studied [6]. Through both physiological and behavioral mechanisms and due to good thermal contact, the human torso provides a strong stabilizing effect on Medipad system operating temperatures. With adequate clothing, the drug chamber temperature should not fall below 29°C under continuous patient exposure to freezing temperatures or during shorter exposure ($<$10 min) to cold temperatures without adequate clothing. With increased ambient temperatures, sweat evaporation limits drug temperature to a maximum of 37.5°C when protected from direct exposure to the sun by minimal covering [7]. Results obtained in these tests are now used to determine temperatures for compound stability and compatibility testing as well as delivery accuracy testing.

Finally, a gas-actuated delivery system must not be subject to changes in barometric pressure. An integral barometric-pressure-compensating valve maintains the internal system pressure at a set level. As a result, the Medipad system maintains a $\pm$10% delivery accuracy across a broad range of barometric pressures and temperatures [8].

Data from this development work were used to finalize the functional specification and to develop the detailed design. Component tooling was developed,

Copyright © 2003 Marcel Dekker, Inc.

and a pilot manufacturing process and facility were established. Each Medipad model was qualified using a broad regimen of in vitro tests with over 400 Medipad systems. Qualification testing included delivery performance under various conditions, shelf life, adhesion, needle performance, load bearing, end-of-delivery indicator, mechanical integrity, transportation and packaging, biocompatibility and toxicity, and sterility. The design is currently in the final stages of technology transfer to a commercial manufacturing facility, which will utilize automated assembly techniques with production capacity in the millions.

V. HUMAN STUDIES

Several pharmacokinetic studies have evaluated the delivery of morphine sulfate as a model compound via the Medipad system. These studies demonstrated delivery at a constant, consistent rate over a 48-h period and illustrated the intersubject variability of the Medipad system as similar to a bolus SC injection [9]. In another comparative morphine pharmacokinetic study shown in Figure 4, the Medipad system was compared to two products: a marketed ambulatory microinfusion

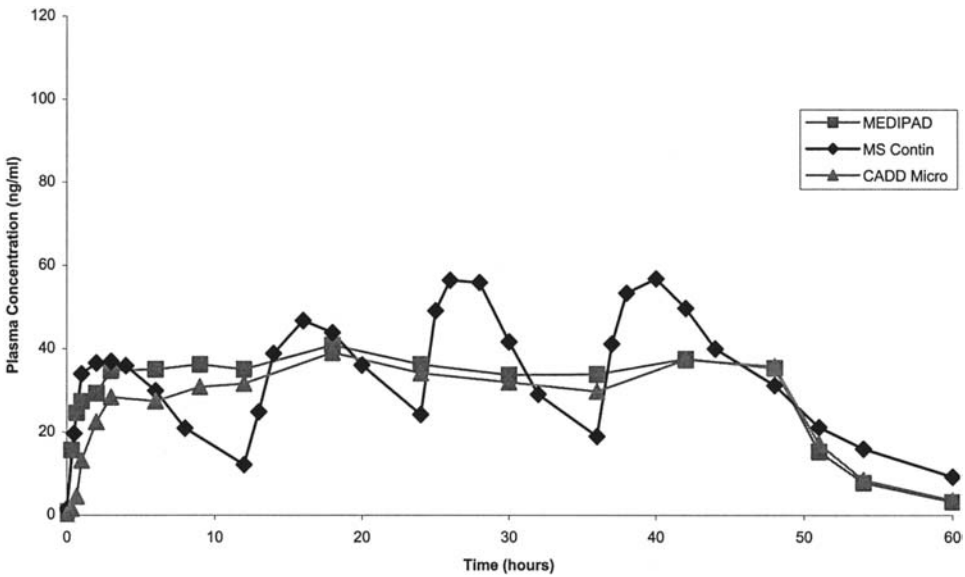


Figure 4 Comparative morphine pharmacokinetic study. Mean morphine plasma concentrations of MSContin® 120 mg every 12 h orally for 48 h versus the Medipad system at 3.45 mg/h SC for 48 h versus the CADD-Micro™ pump at 3.4 mg/h SC for 48 h.

Copyright © 2003 Marcel Dekker, Inc.

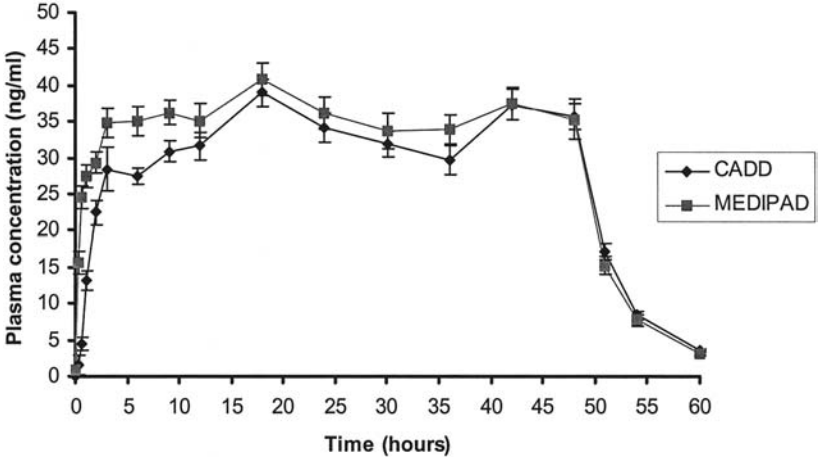


Figure 5 Mean morphine plasma concentrations of 48-h SC morphine infusions via Medipad system and CADD Micro with standard error of mean.

pump with an attached SC microvolume infusion set and an oral, sustained-release morphine. The study demonstrated very similar performance and similar intrasubject and intersubject variability for the two SC microinfusion delivery systems. The mean pharmacokinetic profiles for the two SC delivery systems delivering morphine sulfate as a model compound are shown in Figure 5 [10].

Local application site assessments indicated that the device is well tolerated, with minor, transient erythema reported as the most common adverse event. To date, no severe or serious adverse events have been associated with the system [9]. In a study in elderly subjects performed to evaluate the comfort and tolerability of the Medipad system alone during a 48-h application, the system was well tolerated. On a scale from 0 (extremely comfortable) to 10 (extremely uncomfortable), the highest score was 3, given by only a single subject. Overall 85% of the subjects gave a rating of 0. The majority of the skin site evaluations were reported to be mild, and skin reactions disappeared within 24 h in most subjects [9].

VI. EXAMPLES OF DRUG/CLINICAL APPLICATIONS OF TECHNOLOGY

Potential applications for the Medipad system include compounds with poor oral bioavailability, compounds with a short half-life that would normally require fre-

Copyright © 2003 Marcel Dekker, Inc.

quent dosing, or compounds requiring controlled, prolonged delivery to maintain smooth plasma profiles. Additionally, compounds with a narrow therapeutic window or those requiring fast onset and fast offset are also potential candidates for the system. For injectable formulations with large SC-dosing volumes (e.g., $\geq$1.5 mL), the Medipad system could be used to provide a short infusion over a few hours, facilitating SC absorption.

The Medipad system is not limited to certain drug classes, but can be used with a variety of compounds including peptides, proteins, and other macromolecules. Most often, candidate compounds are macromolecules that are self-administered on an outpatient basis for several weeks or for chronic use. A compound must be stable and compatible with Medipad system fluid path components at an elevated temperature, normally at least twice as long as the use time. Additionally, the amount of drug to be infused should be in a small volume or should have the capability to be concentrated into a few milliliters. During feasibility evaluation, in vitro accuracy testing is performed to ensure delivery is within specification. Finally, the candidate drug must be well tolerated when given subcutaneously.

VII. REGULATORY ISSUES

In the United States, Canada, and Europe, the Medipad system can be used to conduct clinical studies on compounds in development and can also be registered with approved drugs to achieve drug/device combination presentation for commercialization.

As a device, the Medipad system would normally be reviewed by the FDA as a Class II device (infusion pump) subject to 510(k) premarket clearance through FDA's Center for Devices and Radiological Health for administration of approved drugs according to the drug's labeling. However, the Medipad system is intended for commercialization copackaged as a drug/device combination and is most often used with NCEs currently in clinical development.

To support use of the Medipad system in U.S. clinical studies, information and data on the Medipad system are reviewed in the IND process. During clinical trials, the drug therapy, including the Medipad system, is studied for safety and effectiveness. Ultimate registration of the Medipad system and the drug is achieved by filing an NDA. Approval is received for the specific drug/device combination and the product can be marketed as a drug/device combination presentation.

Outside the United States, the Medipad system is an approved medical device for use in Europe as demonstrated by the CE mark accreditation. Certain provisions of the drug and/or device regulations in each European country allow copackaging as a combination product. Clinical studies of drug in development

Copyright © 2003 Marcel Dekker, Inc.

are conducted using the Medipad drug delivery system under the usual drug regulations for each country by referencing the CE mark. The Medipad system has also received approval as a device by Canadian authorities.

VIII. TECHNOLOGY POSITION/COMPETITIVE ADVANTAGE

As compared to depot formulations, the Medipad system can shorten the time to clinical evaluation, as the delivery system is separate from the formulation. As compared to ambulatory infusion pumps, the Medipad system is small, discreet, easy to use, and designed for self-administration by unskilled users in outpatient or home settings to reduce health care costs.

Benefits of the Medipad system include improved bioavailability with SC administration, continuous zero-order delivery for up to 48 h, circumvention of first-pass metabolism, extended bolus duration to improve large SC dose/volume absorption, and factory-set dosing.

IX. FUTURE DIRECTIONS

Future development includes expanding the capabilities of the Medipad system by broadening the range of rates and volumes. Additionally, accessories for user reconstitution of lyophilized compounds and subsequent filling of the Medipad system are also in development.

Linking the Medipad system to sensors that continuously monitor vital signs and adjust the delivery rate is also under investigation, which would enable systems to offer complex delivery profiles. These "smart" systems could then be used for chronotherapeutic delivery or for use with other compounds with complex and variable delivery profiles.

REFERENCES

1. E Meehan, Y Gross, D Davidson, M Martin, IA Tsals. Microinfusor device for the delivery of therapeutic levels of peptides and macromolecules. J Control Rel 46: 107–116, 1996.
2. J Kelly. Delivery of macromolecules. Elan Rev 8–11, 1994.
3. O Cabiri, M Sahar, D Katz, I Tsals. Delivery rate estimation through measurement

---

MEDIPAD™ and Pump-In-A-Patch™ are trademarks of Elan plc. CADD-Micro™ is a trademark of SIMS Deltec, Inc. MSContin® is a trademark of The Purdue Pharma L.P.

Copyright © 2003 Marcel Dekker, Inc.

of Medipad system internal pressures. Proceedings of the 4th World Meeting, APGI/APV, 2000.
4. A O'Connell, D O'Malley, C Wilson, D Katz, M Sahar, M Martin, E Meehan. Microinfusion of sumatriptan from Medipad, a novel delivery system. Proc Int Symp Control Rel Bioact Mater 24:981–982, 1997.
5. I Tsals, Y Gross, M Rozanowich, D Katz, M Sahar. Back pressure during subcutaneous infusion by Medipad drug delivery system. Proc Int Symp Control Rel Bioact Mater 26:1060–1061, 1999.
6. I Tsals, H Danon, D Katz, M Sahar, D Davidson. Thermal evaluation of the Medipad delivery system. Proceedings of the AAPS Annual Meeting and Exposition, 1998.
7. I Tsals, R Goldman, H Danon, J Gross, M Sahar. Effects of ambient temperature on MEDIPAD operation. Proceedings of the 2nd World Meeting APGI/APV, Paris, May 24–28, 1998.
8. M Sahar, D Katz, I Tsals, G Shtepel, K Barton. In-vitro performance of the Medipad delivery system at extreme environmental conditions. Proceedings of the AAPS Annual Meeting and Exposition, 1999.
9. Data on file, Elan Pharmaceutical Technologies.
10. P Lynch, J Butler, D Huerta, I Tsals, D Davidson, S Hamm. A pharmacokinetic and tolerability evaluation of two continuous subcutaneous infusion systems compared to an oral controlled-release morphine. J Pain Symp Manage 19:348–356, 2000.

Copyright © 2003 Marcel Dekker, Inc.

61
Intranasal Drug Delivery

Daniel P. Wermeling and Jodi L. Miller
University of Kentucky, Lexington, Kentucky, U.S.A.

I. INTRODUCTION

Over half a century ago, Noah Fabricant stated, "The use of nasal medication has never been as widespread and popular as it is today. . . . Nasal medication actually may be considered tapping on the door of maturity. The tapping should grow louder, for there is ample evidence to demonstrate that it will continue to improve with the passing of time" [1]. Now, almost 60 years later, these sentiments still ring true. In the year 2000, there were 27 products on the U.S. market for intranasal use, with more than half of these obtaining Food and Drug Administration approval between 1990 and 2000. The market value of these products was estimated to be 1.5 billion dollars [2]. With ever-increasing pharmaceutical technology and numerous medicinal opportunities for intranasal administration, its popularity will most likely continue.

Depending on the therapeutic intent, intranasal drugs may be targeted for local treatment or systemic action. The majority of products currently marked in the United States for local effects are steroidal agents for treatment and prevention of nasal symptoms. Intranasal drugs for systemic action include treatments for migraine headaches, calcium supplementation, vitamin B_{12} deficiency, and pain relief, as well as other therapeutic indications [2]. The variety of agents currently available is impressive; however, the list of nasal products should expand drastically over the next few years. This chapter will mainly focus on intranasal products designed for systemic delivery. In addition to either local or systemic effects, agents may be intended for acute or chronic treatment. The expected duration of treatment and therapeutic use will also impact product design.

Copyright © 2003 Marcel Dekker, Inc.

Nasal administration offers many benefits compared to alternate delivery routes. Not only is the nasal cavity easily accessible, it is virtually noninvasive. In most cases intranasal administration is well tolerated; however, depending on the substance delivered, slight momentary irritation may occur. Owing to the nasal cavity's extensive vascular supply, absorption rates and onset of action for systemic medications are comparable to injectable administration routes yet the need for needles is eliminated. In addition, hepatic first-pass metabolism is avoided with intranasal delivery and destruction of drugs by gastric fluid is not a concern.

II. NASAL ANATOMY AND PHYSIOLOGY

The basic nasal structures are shown in Figure 1 [3]. The distance from the tip of the nose to the pharyngeal wall is about 10–12 cm [4]. The nasal septum divides the nose into two nasal cavities, each with a 2–4-mm-wide slit opening [4]. Each cavity has a surface area of approximately 75 cm^2, a volume of 7.5 mL, and contains three distinct functional regions [5]. The vestibular region is located closest to the nasal passage opening, contains long hairs, and serves as a filter for incoming particles [6]. The respiratory region, containing the largest surface area, is located between the vestibular and olfactory regions [6]. The

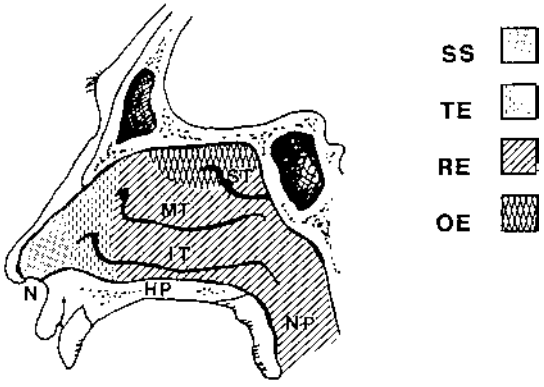


Figure 1 Diagrammatic representation of the exposed mucosal surface of the nasal lateral wall and turbinate of the human. Distribution of the four epithelial populations is also shown. SS, squamous epithelium; TE, transitional (nonciliated, cuboidal) epithelium; RE, respiratory epithelium; OE, olfactory epithelium; N, nares; HP, hard palate; NP, nasopharynx; ST, superior turbinate; MT, middle turbinate; IT, inferior turbinate. (Modified from Ref. [3] with permission.)

Copyright © 2003 Marcel Dekker, Inc.

respiratory region is considered the most important section for delivering drugs systemically and will be discussed in more detail below [5]. Finally, the olfactory region is located in the uppermost portion of each cavity and opposite the septum [5,6]. This is the region responsible for functions associated with smell.

The epithelium of the respiratory region consists of four different cell types (Fig. 2): basal, mucus-containing goblet, ciliated columnar, and nonciliated columnar [5,7]. The ciliated columnar cell is the most predominant. The cilia beat in a wave-like, coordinated manner to transport mucus and trapped particles to the pharynx area for subsequent ingestion [5,6]. Cells in the respiratory region are covered by approximately 300 microvilli, which greatly increase the surface area of the nasal cavity [5]. The respiratory region also contains the inferior, middle, and superior turbinates [5]. The lamina propria, below the epithelium, houses blood vessels, nerves, and both serous and mucus secretory glands [7].

Blood is delivered to the nose from the external and internal carotid arteries [5,8]. The lateral and medial nasal walls are directly supplied by the sphenopalatine artery, which is a distant branch of the external carotid [8]. These sections of the nose are drained by the sphenopalatine foramen [5]. The anterior section of the nose receives blood from the ophthalmic arterial branch of the internal carotid and is drained via the facial vein [5,8]. The lamina propia contains a dense network of capillaries, including many very permeable fenestrated capillaries [4,8].

The vidian nerve provides the majority of cholinergic innervation to the nasal cavity. When stimulated, acetylcholine is released and vasodilatation occurs

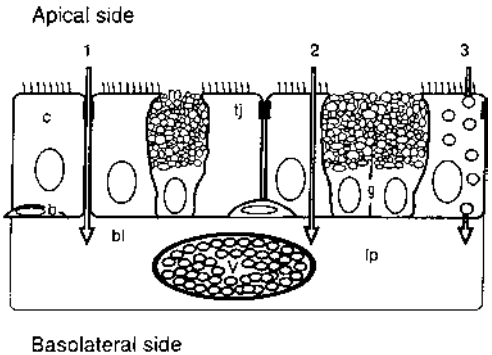


Figure 2 Schematic representation of transport routes across nasal respiratory epithelium: (1) paracellular; (2) transcellular; (3) transcytotic. Goblet cells (g), ciliated columnar cells (c), and tight junctions (tj) are presented. Basal cells (b) are located on the basal lamina (bl) adjacent to the lamina propia (lp) with blood vessels (v). (From Ref. [48] with permission.)

Copyright © 2003 Marcel Dekker, Inc.

[4]. Sympathetic innervation to the nose arises from the stellate ganglion [4]. Released norepinephrine acts on both α and β_2 receptors and the overall result is vasoconstriction, demonstrating dominance of the α receptor [4].

A mucus layer, resulting from nasal and lacrimal gland secretions as well as plasma transudate, is present on the nasal passage epithelium [7–9]. The pH of secretions ranges from 5.5 to 6.5 and from 5.0 to 6.7 in adults and children, respectively [10]. The mucus consists of an outer viscous layer of mucus (gel) and a watery (sol) layer located along the mucosal surface [8,9]. Glycoproteins, particularly mucin, are responsible for the gel-like appearance of the mucus. Lysozymes, enzymes, and immunoglobulins in addition to other proteins may also be found in the mucus. Approximately 3% of the mucus consists of these proteins while the remainder is made of 90–95% water and 1–2% salt. Each day about 1500 to 2000 mL of mucus is produced [7,8]. The epithelium is covered with a new mucus layer approximately every 10 min [8].

Mucosal clearance is an important defense function of the nasal passage. Clearance occurs as a combined effort of the mucus layer and cilia action. The cilia project into the sol layer where they move in a sweeping motion back and forth. The gel layer of the mucus, along with entrapped particles, is transported to the nasopharyngeal area for ingestion [7]. The cilia beat at a frequency of approximately 10–13 Hz [11,12]. This results in the movement of mucus at a rate of approximately 5–6 mm/min and therefore clearance of particles from the nose within 20 min [4,9].

Xenobiotic-metabolizing enzymes are present in the nasal mucosa [8,9, 13–19]. In animals, these enzymes are found in greater quantities in the olfactory epithelium compared to the respiratory epithelium of the nose. In humans, this distinction remains unclear owing to difficulty obtaining olfactory epithelium [13,14]. In the respiratory mucosa of humans, the concentration of cytochrome P450 enzymes is 25 pmol/mg of microsomal protein [19]. Isoforms of the P450 enzyme that have been identified in humans thus far include CYP1A, CYP2A, and CYP2E [14]. Carboxylesterases, glutathione S-transferases, and rhodanese enzymes have also been detected in the human nasal mucosa [20–23].

Normal physiology of the nasal passage is subject to alteration as a result of many environmental and pathological factors. Some of these are encountered quite frequently in the general population, including the common cold and other respiratory viruses [24], allergic [25–30] and nonallergic rhinitis [31,32] as well as treatment of these conditions, smoking [33,34], and the process of aging [35]. Additionally, although some conflict exists in the medical literature, estrogen is believed to induce physiological changes in the nose [36–43]. Alterations in the nasal cavity may also be caused by the presence of a deviated septum [44], immotile cilia syndrome [45], or nasal polyps [46]. The potential effects of these modifications on local drug action or systemic exposure should be taken into account when considering intranasal administration.

Copyright © 2003 Marcel Dekker, Inc.

III. INTRANASAL DRUG ABSORPTION

To reach the vascular system substances intended for systemic absorption must first pass through the mucus layer followed by the epithelium. A review by Khanvilkar et al. [47] addresses the numerous issues associated with drug transfer through mucus. The mucus does not present a major problem for small, uncharged particles. On the other hand, some larger or charged molecules may encounter difficulties passing through this layer. One important rate-limiting factor in the diffusion of drug through the mucus is potential binding of solutes to mucin. Types of interactions between foreign molecules and the mucus include electrostatic, hydrophobic, and van der Waals. In addition, the mucus' structure is very sensitive to its environment, meaning that alterations in pH, temperature, osmotic pressure, etc. may induce structural changes in this layer. This dynamic nature of the mucus may cause variations in the transfer of molecules from the delivery site to the epithelium [47].

Once a substance passes through the mucus, it may cross the nasal mucosa by three different mechanisms (Fig. 2) [48]. First, it may be transferred via transcellular, or simple, diffusion across the membrane by way of pores or carriers [18,49]. A second method is paracellular transport, which involves movement through the spaces between cells and tight junctions [18]. This pathway is believed to be important for absorption of peptides and proteins [50,51]. The third mechanism is transcytosis. This entails particle uptake into vesicles, subsequent transfer across the cell, and, finally, deposition into the interstitial space [49].

In addition to passing through the mucus layer and penetration through the epithelium, substances may undergo metabolism by nasal enzymes present in the mucosa. Also, because of normal physiological mucocilliary clearance mechanisms, drugs have limited absorption time in the nasal cavity. Both of these are important factors to keep in mind for intranasal drug absorption. Furthermore, it has also been suggested that redistribution of molecules within the nasal mucosa is a possibility [51]. This recycling effect would be beneficial for topical agents; however, it may affect the absorption kinetics for drugs intended for systemic action.

Pharmacokinetic parameters following intranasal absorption will vary with administration of different agents. Values in the literature for time to reach maximum concentration in humans range from 5 min to 4 h [52–59]. Also, bioavailability with intranasal delivery greatly varies and is dependent on numerous factors such as the drug itself, formulation differences, and the delivery system, all of which will affect nasal exposure, extent of absorption, and the pharmacokinetics of each particular agent or formulation.

One last consideration for intranasal absorption is the potential transfer of substances from the nasal cavity directly to the central nervous system (CNS). This topic has been reviewed elsewhere in the scientific literature [56]. In rats,

Copyright © 2003 Marcel Dekker, Inc.

CNS uptake of fluorescein-isothiocyanate-labeled dextrans of differing molecular weights (4400–40500 Da) [60], ^{3}H-dihydroergotamine [61], and ^{3}H-5-fluorouracil [62] following intranasal and intravenous (IV) administration has been studied. Sakane et al. [60] found undetectable levels of all the dextrans studied in the cerebrospinal fluid (CSF) after the IV dose. However, levels were detectable for dextrans with a MW $\leq$20,000 Da in the CSF with intranasal administration. Wang et al. [61] found comparable or greater levels of radiolabeled dihydroergotamine in different regions of the brain with IV and intranasal administration despite lower intranasal plasma radioactivity concentration-time profiles. Sakane et al. [62] observed significantly higher ratios for CSF/plasma and cerebral cortex/plasma concentrations with intranasal instillation as compared to IV infusion. Observations from these three investigations suggest a direct pathway does exist from the nasal cavity to the CNS.

Three potential mechanisms exist for the delivery from the nose to the brain. First, drug that reaches the systemic circulation may then subsequently cross the blood-brain barrier. Second, substances may cross the olfactory epithelium via simple diffusion, receptor-mediated transcytosis, or paracellular transport. The substance may then follow the nerve to the CNS or gain entry to the lamina propria. From the lamina propria, drugs may enter either the lymphatic system or systemic circulation [6]. Third, an agent may be taken up by a neuronal cell of the olfactory nerve, undergo intracellular axonal transport, and gain entry to the brain via the olfactory bulb [5,6]. The possibility of direct penetration into the CNS may be desirable for some agents; however, it may be problematic for others.

IV. CONSIDERATIONS FOR INTRANASAL PRODUCT DESIGN

A. Drug Formulation

Many factors play a role in the absorption of substances from the nasal cavity. These factors mostly center on the chemical attributes of a particular agent, the excipients in the formulation, and means of delivery. Molecular weight is believed to offer the best correlation with extent of absorption [50,63]. Agents with a molecular weight less than 1000 are absorbed to a much larger degree than agents with molecular weights greater than 1000. For larger molecules, the addition of an adjuvant may be useful [49]. Not only is molecular weight important in absorption, but also the molecular size and shape of an agent. Cyclic-shaped molecules are better absorbed than those having a linear structure [49]. Particle size is also important because spray particles less than 10 μm may bypass the nasal cavity and be deposited in the lungs [12]. For powder formulations, a parti-

Copyright © 2003 Marcel Dekker, Inc.

cle size of greater than 50 μm has been shown to provide a favorable pattern of distribution in the nose [64].

Systemic bioavailability decreases as the hydrophilicity of an agent increases [65]. Bioavailability is affected by pH and pKa factors as well [66–69]. The pH of the drug, formulation, and nasal cavity all need to be taken into account. It is generally well known that un-ionized chemical species are capable of moving across membrane barriers more readily than ionized species, and thus, increased absorption usually occurs. However, drug formulations should not be extremely acidic because they may cause damage to the nasal epithelium and surface enzymes [67,69]. Although increased absorption could result from the structural damage, nasal integrity should not be compromised. Designing formulations so the final pH is within a range of 4.5–6.5 is suggested to minimize nasal irritation [68]. Another formulation factor to consider is osmolarity. In one study, when the osmolarity of the solution was adjusted with mannitol greater biological activity of the delivered agent was observed [68]. Additionally, a study in rats demonstrated a solution of 0.462 M provided the best absorption of secretin although shrinkage of epithelial cells was observed [66].

Other elements to consider when designing agents for intranasal administration are the solution concentration and volume to be delivered. One study focused on intranasal insulin delivery determined a higher concentration did not produce significantly greater activity [70]. On the other hand, the initial drug concentration has been found to influence nasal absorption [9,71]. Larger delivery volumes allow better distribution and coverage of the nasal passage, which theoretically would lead to greater drug absorption. One study suggests a larger volume with a weaker concentration is preferable to a small, very concentrated volume [9,72]. Another study demonstrated higher plasma peak levels and biological response when the total spray volume delivered per nostril (100 μL) was delivered as two separate sprays (50 μL each) [73]. The volume that can be reasonably delivered is also limited by the size of the nasal cavity. Behl et al. [68] suggest an upper limit of 25 mg/dose and a volume of 25–150 μL/nostril.

Since the normal physiological process of the nose, i.e., mucocilliary clearance, is critical to its defense mechanisms, disruption should be avoided. Substances delivered to the nasal cavity may cause inhibition of this system or enhance the clearance process [7,74]. Enhancing this process in most cases would be undesirable because the time for drug absorption would decrease. So the potential nasal physiological effects a drug or formulation excipient may have must be considered as well. This should especially be evaluated for drugs intended for chronic therapy so prolonged mucosal dysfunction is avoided.

Another relevant formulation issue for intranasal products is maintenance of sterility. A very common preservative, benzalkonium chloride, has been added to numerous nasal products [75]. Despite its popularity, reports in the literature

Copyright © 2003 Marcel Dekker, Inc.

suggest it may be associated with hypersensitivity reactions [76], mucosal swelling [77,78], and decreased mucocilliary transport [75]. Since many nasal products are multidose open systems, a preservative of some sort is necessary. An alternative for multidose packages may be delivery with a nasal spray bottle filled under aseptic conditions and designed to prohibit contamination upon use [79]. Unit-dose systems have an advantage over multidose because no preservative is required as long as the product undergoes sterile fill processing. The sterile fill process may include filtration or the use of terminal sterilization procedures.

One must also keep in mind patient acceptability especially for agents intended for chronic therapy [84]. Some formulations may cause transient discomfort upon instillation. This discomfort may be related to the drug, for example midazolam [81], or to inactive excipients such as propylene glycol [82,83]. If a product causes irritation or distress during application, patient compliance will most likely be compromised.

The discussion above has focused on formulation issues related to agents intended for systemic delivery. For local residence and effect in the nasal cavity there are other considerations. Of course, many of the items previously presented are important for either type of delivery. These include compatibility with the nasal tissue, for example, and appropriate pH and osmolarity, careful choice of a preservative if needed, and a reasonable concentration and volume for administration. Additionally, drugs for local effect may be targeted to a specific area of the nasal cavity rather than general distribution. An example of this is treatment of nasal polyposis where the target area for drug disposition is the sinus mucosa [84]. Aqueous formulations are desirable for local delivery. If the drug molecule is highly water-insoluble, it may be necessary to use wetting agents such as polysorbate 20 and sorbitan laurate to develop an aqueous suspension [84]. Using this type of method, undissolved drug should be available at the local site of action [84].

B. Dosage Form

Besides chemical and formulation issues, the dosage form is also important for intranasal administration. To date, delivery of substances to the nose has been via insufflation of powders, topical gels, sprays, drops, and nasal pledgets [9,50,52]. One study has shown sprays to significantly increase bioavailability even when compared to powder formulations [80]. Alternatively, powders appear to offer many benefits such as increased chemical stability, decreased need for preservative additions, administration of larger doses, and in some cases, greater bioavailability and absorption [64]. The choice of dosage form and the delivery system employed should be focused on feasibility and chemical stability, and should compliment the expected therapeutic use. Table 1, based upon a review

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Important Considerations for Intranasal Dosage Forms

Dosage form	Key points
Nasal drops	Best for solutions
	Metering of doses may be inaccurate or inconsistent
Solution spray	Metered-dose actuator devices are available
	Accurate dosing is feasible with spray devices
Suspension spray	Metered-dose actuator devices are available
	Orifice of the actuator may need modification for proper delivery
	Common dosage form for local effects
Powders	May cause irritation and leave gritty sensation
	Greater expense for drug development
Gels	Metered-dose devices are available
	Postnasal drip and anterior leakage are decreased
	Used for systemic and local drug delivery
Emulsions/ointments	Best for local action
	Patient acceptability is low
	Difficult to provide accurate dose

Source: Based on Ref. [68].

by Behl et al. [68], contains a brief list of various intranasal dosage forms along with key considerations.

C. Delivery Device

The delivery device for a particular formulation should be based on several factors, including accuracy and dose reproducibility, cost, simple use for the patient, physiochemical characteristics of the drug and chosen dosage form, and protection from microbial contamination [85]. Metered-dose systems are considered the best for dose accuracy and reproducibility. Current delivery devices for liquid and powder intranasal formulations are the following [85]:

Liquid formulations—instillation catheter, dropper, unit-dose containers, squeeze bottle, pump spray, airless and preservative-free sprays, compressed air nebulizers, and metered-dose inhalers

Powder formulations—insufflators, monodose inhalers, multidose inhalers, and pressurized metered-dose inhalers

The delivery device and drug formulation should also be compatible with each other to prevent leaching and absorption, which could pose a risk for toxicity

Copyright © 2003 Marcel Dekker, Inc.

and may affect dose accuracy, respectively. Additionally, a device should be chosen on its ability to store the formulation appropriately without compromising stability [85].

V. TECHNOLOGIES FOR MODIFIED INTRANASAL DRUG DELIVERY

Modifications of intranasal delivery formulations primarily include the addition of absorption enhancers to increase bioavailability and the use of bioadhesive delivery systems to prolong drug contact time in the nasal passage for both increased and sustained drug release [50]. These technologies are expanded upon below. Absorption enhancers as well as bioadhesive systems have moved closer to the forefront of pharmaceutical research when the nasal cavity was targeted as a prime delivery route for proteins and peptides. These modifications attempt to minimize the physiological barriers encountered in the nose. Barriers to drug absorption are a limited residence time in the nasal cavity due to mucocilliary clearance, penetration through and possible interaction with the mucus layer, passage of large molecules across the epithelial layer, and avoidance of potential enzymatic degradation.

The broad category of absorption enhancers includes compounds that can be divided into the following classes: surfactants, glycosides, bile salts, chelators, fatty acid salts, fusidic acid derivatives, phospholipids, glycyrrhetinic acid derivatives, cyclodextrins, glycols, cyclic peptide antibiotics, preservatives, carboxylic acids, and O-acyl carnitine derivatives [50]. Selected enhancer agents will be discussed in more detail below. These enhancers may improve the absorption of substances using a variety of mechanisms such as increasing membrane fluidity, paracellular or transcellular transport, and nasal blood flow, or decreasing mucus layer viscosity, inhibiting proteolytic enzymes, loosening the tight junctions between epithelial cells, dissociating protein aggregation, and initiating membrane pore formation [50]. One, or a combination, of these methods may be used to enhance drug absorption.

Cyclodextrin and its derivatives appear to be the best-studied category of enhancers. Cyclodextrins are cyclic oligosaccharides consisting of an inner hydrophobic core and an outer hydrophilic surface. This composition allows the formation of inclusion complexes with lipophilic compounds [86]. The mechanisms of action of cyclodextrins include solubilization and stabilization of peptides and proteins, prevention of aggregation and proteolytic degradation, and the opening of tight epithelial junctions [86,87]. Of the numerous cyclodextrin derivatives, dimethyl-β-cyclodextrin has been found the most effective for improving nasal bioavailability while minimizing toxic potential [80,88]. Cyclodex-

Copyright © 2003 Marcel Dekker, Inc.

trins have been used successfully to increase the absorption of many substances including, but not limited to, luteinizing hormone-releasing hormone [88], biosynthetic human growth hormone [89–93], ACTH(4–9) peptide analog [94], and salmon calcitonin [95].

Enzyme inhibitors, specifically targeting aminopeptidase, have been effective in promoting the nasal absorption of a variety of peptides [50]; however, findings of Machida et al. [96] suggest the effectiveness of recombinant human granulocyte colony-stimulating factor was not enhanced with the addition of an enzyme inhibitor. Also, aprotinin, camostat mesilate, and soybean trypsin inhibitor were studied for their absorption enhancing effects on intranasal vasopressin and its 1-deamino-8-D-arginine analog [97]. Only camostat mesilate, an inhibitor of both aminopeptidase and trypsin, was found to significantly increase the biological effects. Thus, enzyme inhibitors seem to vary in their degree of effectiveness.

Other absorption enhancers have also proven to be useful as described here in brief detail. A medium-chain phospholipid enhanced intranasal insulin pharmacokinetics with minimal nasal irritation [98]. Laureth-9 also aids in the absorption of insulin [99]. Lauroylcarnitine chloride was found beneficial in rats for increasing salmon calcitonin absorption [100]. Glycyrrhetinic acid derivatives, especially carbenoxolone disodium salt, enhanced insulin uptake without nasal irritation or insulin degradation [101]. In sheep, both sodium deoxycholate and polyoxyethylene 9-lauryl ether enhanced nasal absorption of interferon [102]. Finally, sodium taurodihydrofusidate (STDHF) was found useful in rabbits and rats for increasing bioavailability of insulin [103]. The absorption-enhancing effect of STDHF has been shown to increase as its concentration increases and to promote absorption independently of penetrant molecular weight [104]. Despite its potential usefulness as an absorption enhancer, toxic effects on the nasal mucosa may prevent its use therapeutically [105]. As with all components of nasal formulations, preservation of physiological processes is desirable.

The other major modification for intranasal formulations is the use and incorporation of bioadhesive technology. Recent reviews of this technology in association with nasal delivery are available in the medical literature [85,106]. Bioadhesion refers to the adherence of a compound to biological material through interfacial forces. The bioadhesive compound then remains attached for a prolonged period of time [106]. The term "mucoadhesion" is used when the compound binds to the mucus covering of a biological tissue [85]. As described by Illum [106], a series of steps occurs during this process. First, the bioadhesive agent and membrane/mucus layer need to come into contact with each other. Then, the chains of the adhesive agent penetrate into the membrane crevices or interpenetration with mucosal chains occurs. Thus, increased residence time within the nasal cavity allows for more complete, as well as prolonged, absorp-

Copyright © 2003 Marcel Dekker, Inc.

tion. These agents may also inhibit enzymatic activity and have demonstrated the ability to cause alterations in the tight junctions, leading to increased substance penetration [85].

The most common polymers used for intranasal delivery are carbopol, cellulose compounds, sodium hyaluronate, polycarbophil, starch, dextran, and chitosan [106]. These may be delivered to the nasal passage via several systems including liquid solutions, gel, powder, and microspheres [106]. Several factors are important for the effectiveness of a bioadhesive material. Both the chemical class of a polymer and its polymer molecular mass are important to its bioadhesive characteristics. Each class has a critical mass value where adhesiveness is at an optimum level [85]. Also, penetration via the bioadhesive chain is extremely important to its binding ability; therefore, extensive or dense cross-linking is not desired [85]. Similar to having an optimum mass for bioadhesive properties, the polymer concentration at the targeted interface may also affect binding ability [85,106]. Other considerations for bioadhesive efficacy include the level of hydration and the pH of the environment. Too much hydration will cause excessive swelling of the polymer and subsequently decrease adhesion. Also, changes in the nasal pH may alter the bioadhesive binding effectiveness via alteration of charge potential and interactions [85].

The most predominant polymer used for bioadhesion is chitosan. Chitosan and its use as a delivery system has been recently reviewed by Janes et al. [107]. This polymer is obtained by deacetylation of chitin, which is naturally found in crab and shrimp shells [108]. Chitosan is a high-molecular-weight, cationic, hydrophilic polymer. It is biodegradable and has low toxicity [109–111]. Increased absorption obtained with chitosan is the result of both bioadhesion and alteration of the tight junctions [112]. Chitosan microspheres and nanoparticles have been used successfully in rabbits for insulin delivery [112,113]. In rats and sheep, a solution formulation of chitosan was found to promote absorption of insulin with little change on the nasal mucosa [109]. Chitosan microspheres have also been studied for systemic delivery of pentazocine [110]. Intranasal pentazocine bioavailability was improved with sustained blood level profiles. An additional use that has been investigated for chitosan is its ability to increase immunogenicity of mucosal vaccines [111]. The clearance of chitosan from the nasal cavity in both a solution form and as microspheres was investigated in humans [114]. The clearance half-lives of the chitosan solution and microspheres were 41 and 84 min, respectively. The half-life of clearance for the control was only 21 min. These studies substantiate chitosan's usefulness as a bioadhesive agent.

In the same study discussed above [114], the clearance of starch microspheres was also evaluated. The clearance half-life for the starch microspheres was 68 min, which was approximately three times the value of the control group. The starch microsphere system was studied for its impact on nasal absorption of desmopressin in sheep [115]. Compared to the control nasal solution, the starch

Copyright © 2003 Marcel Dekker, Inc.

system provided significantly shorter time to maximum concentration (T_{max}), higher maximum concentration (C_{max}), increased area under the curve (AUC), and improved bioavailability. The starch microsphere system is considered relatively safe for drug delivery [116].

Carbopol formulations also appear to be effective for promoting nasal drug exposure. Carbopol 971P, its analog Carbopol 974P, and polycarbophil were evaluated in rabbits for intranasal pharmacokinetics of apomorphine [117]. For all formulations, an increase in drug loading created a trend of increased C_{max} and AUC values as well as decreased T_{max}. Carbopol 971P was further investigated alone and in combination with apomorphine for its potential adverse effects on ciliary beat frequency [118]. Carbopol 971P alone caused partially reversible ciliary inhibition at 0.1 and 0.5% w/v formulations. Additionally, severe inflammation was observed with continued treatment. The investigators conclude Carbopol 971P is not suitable for intranasal administration of apomorphine. Another report focuses on the use of Carbopol 934P for its rheological properties [119]. It has low-viscosity-fluid characteristics, so it may be delivered via nasal spray. Once in the nasal cavity, it transforms into a high-viscosity gel. With this type of Carbopol 934P system, resulting pharmacokinetic parameters for propanolol were favorable in beagle dogs [119]. Carbopol systems appear to be useful bioadhesive agents; however, their nasal safety profiles should be thoroughly investigated prior to therapeutic use.

Other bioadhesive materials have been studied as well. Carboxymethylcellulose was determined to be a safe system for short-term intranasal use [120]. Also, it was found effective for providing sustained release of apomorphine in rabbits [121]. A combination of polymethacrylic acid and polyethylene glycol has been evaluated for its effects on intranasal budesonide delivery in rabbits [122]. Concentrations in the blood remained constant for approximately 45 min after administration. Another bioadhesive delivery system recently evaluated is comprised of esterified hyaluronic acid (HYAFF) microspheres [123]. This system was used in the formulation of influenza vaccines. Significantly increased antibody responses (IgG and IgA) were obtained in mice, rabbits, and micropigs. The intranasal immune response in pigs using the HYAFF system was greater than that observed when given by intramuscular injection. Copolymers of poly (acrylic acid) and pluronic surfactants have recently been developed [124]. This combination utilizes both bioadhesion and thermogelling properties. Residence time of the copolymer in rats was enhanced compared to either methodology alone. Another system, gelatin microspheres, provided desirable absorption of intranasal salmon calcitonin [125]. Additionally, gelatin microspheres demonstrated usefulness for nasal administration of levodopa [126]. An initial fast release was observed followed by a slower release.

Additional systems for increasing residence time and absorption following intranasal administration are emulsion formulations [127–129], liposome [130]

Copyright © 2003 Marcel Dekker, Inc.

and proliposome [131] formulations, and the use of nanoparticles [132,133]. Finally, a sucrose acetate isobutyrate delivery system has been utilized for intranasal vaccination. The addition of this nonpolymeric high-viscosity agent resulted in enhanced immune responses in adult horses [134].

These systems, as well as those previously addressed, demonstrate the wide array of formulation opportunities for intranasal delivery. The main focus of these and future systems should continue on its current path for modifications capable of increasing absorption in addition to providing sustained release.

VI. FUTURE PROSPECTS FOR INTRANASAL DRUG DELIVERY

Currently, the majority of intranasal products on the market are targeted toward local relief or the prevention of nasal symptoms. The trend toward the development of intranasal products for systemic absorption should rise considerably over the next several years. The development of these products will be in a wide variety of therapeutic areas from pain management to treatment for erectile dysfunction. However, the primary focus of intranasal administration, correlated with increasing molecular scientific knowledge and methods, will be the development of peptides, proteins, recombinant products, and vaccines. The nasal cavity provides an ideal administration site for these agents because of its accessibility, avoidance of hepatic first-pass metabolism, and large vascular supply. Future technologies in the intranasal arena will be concentrated on improved methods for safe, efficient delivery systems primarily for molecular agents, but also for numerous therapeutic categories.

REFERENCES

1. ND Fabricant. Nasal Medication. Baltimore, MD: Waverly Press, 1942, pp. 1–3.
2. J Law. Not to be sniffed at. Scrip Magazine May: 35–38, 2000.
3. JR Harkema. Comparative pathology of the nasal mucosa in laboratory animals exposed to inhaled irritants. Environ Health Perspect 85:231–238, 1990.
4. N Mygind, A Änggård. Anatomy and physiology of the nose—pathophysiologic alterations in allergic rhinitis. Clin Rev Allergy 2:173–188, 1984.
5. L Illum. Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 11:1–18, 2000.
6. S Mathison, R Nagilla, UB Kompella. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J Drug Target 5:415–441, 1998.
7. NGM Schipper, JC Verhoef, FWHM Merkus. The nasal mucocilliary clearance: relevance to nasal drug delivery. Pharm Res 8:807–814, 1991.

Copyright © 2003 Marcel Dekker, Inc.

8. YW Chien, S Chang. Intranasal drug delivery for systemic medication. Crit Rev Ther Drug Carr Syst 4:67–194, 1987.
9. YW Chien, KSE Su, S Chang. Nasal Systemic Drug Delivery. New York: Marcel Dekker, 1989, pp. 1–38.
10. SS Hehar, JDT Mason, AB Stephen, N Washington, NS Jones, SJ Jackson, D Bush. Twenty-four hour ambulatory nasal pH monitoring. Clin Otolaryngol 24:24–25, 1999.
11. GSMJE Duchateau, K Graamans, J Zuidema, FWHM Merkus. Correlation between nasal ciliary beat frequency and mucus transport rate in volunteers. Laryngoscope 95:854–859, 1985.
12. NS Jones, S Quraishi, JDT Mason. The nasal delivery of systemic drugs. Int J Clin Pract 51:308–311, 1997.
13. CJ Reed. Drug metabolism in the nasal cavity: relevance to toxicology. Drug Metab Rev 25:173–205, 1993.
14. JR Thornton-Manning, AR Dahl. Metabolic capacity of nasal tissue interspecies comparisons of xenobiotic-metabolizing enzymes. Mutat Res 380:43–59, 1997.
15. AR Dahl, JL Lewis. Respiratory tract uptake of inhalants and metabolism of xenobiotics. Annu Rev Pharmacol Toxicol 32:383–407, 1993.
16. J Jenner, GH Dodd. Xenobiotic metabolism in the nasal epithelia. Drug Metab Drug Interact 6:123–148, 1988.
17. MA Sarkar. Drug metabolism in the nasal mucosa. Pharm Res 9:1–9, 1992.
18. VH Lee. Enzymatic barriers to peptide and protein absorption. Crit Rev Ther Drug Carr Syst 5:69–97, 1988.
19. PG Gervasi, V Longo, F Naldi, G Panattoni, F Ursino. Xenobiotic-metabolizing enzymes in the human respiratory nasal mucosa. Biochem Pharmacol 41:177–184, 1991.
20. JL Lewis, KJ Nikula, R Novak, AE Dahl. Comparative localization of carboxylesterase in F344 rat, beagle dog, and human nasal tissue. Anat Rec 239:55–64, 1994.
21. A Aceto, CD Ilio, S Angelucci, V Longo, PG Gervasi, G Federici. Glutathione transferases in human nasal mucosa. Arch Toxicol 63:427–431, 1989.
22. NSR Krishna, TV Getchell, YC Awasthi, N Dhooper, ML Getchell. Age- and gender-related trends in the expression of glutathione S-transferases in human nasal mucosa. Ann Otol Rhinol Laryngol 104:812–822, 1995.
23. JL Lewis, CE Rhoades, PG Gervasi, WC Griffith, AR Dahl. The cyanide-metabolizing enzyme rhodanese in human nasal respiratory mucosa. Toxicol Appl Pharmacol 108:114–120, 1991.
24. B Winther. Effects on the nasal mucosa of upper respiratory viruses (common cold). Dan Med Bull 41:193–204, 1994.
25. A Togias, RM Naclerio, D Proud, U Pipkorn, R Bascom, O Ilioupoulos, A Kagey-Sobotka, PS Norman, LM Lichtenstein. Studies on the allergic and nonallergic nasal inflammation. J Allergy Clin Immunol 81:782–790, 1988.
26. RM Naclerio. Pathophysiology of perennial allergic rhinitis. Allergy 52(suppl 36): 7–13, 1997.
27. AK Badhwar, HM Druce. Allergic rhinitis. Med Clin North Am 76:789–803, 1992.
28. D Wang, P Clement. Pathogenic mechanisms underlying the clinical symptoms of allergic rhinitis. Am J Rhinol 14:325–333, 2000.

Copyright © 2003 Marcel Dekker, Inc.

29. H Klementsson. Eosinophils and the pathophysiology of allergic rhinitis. Clin Exp Allergy 22:1058–1064, 1992.
30. R Naclerio, W Solomon. Rhinitis and inhalant allergens. JAMA 278:1842–1848, 1997.
31. G Philip, AG Togias. Nonallergic rhinitis. Eur Arch Otorhinolaryngol 252(suppl 1):S27–S32, 1995.
32. A Sanico, A Togias. Noninfectious, nonallergic rhinitis (NINAR): considerations on possible mechanisms. Am J Rhinol 12:65–72, 1998.
33. M Englender, D Chamovitz, M Harell. Nasal transit time in normal subjects and pathological conditions. Otolaryngol Head Neck Surg 103:909–912, 1990.
34. EJ Kaminski, OE Fanher, CJ Calandra. In vivo studies of the ciliostatic effects of tobacco smoke. Arch Environ Health 16:188–193, 1968.
35. DR Edelstein. Aging of the normal nose in adults. Laryngoscope 106(suppl 81): 1–25, 1996.
36. A Molteni, RL Warpeha, L Brizio-Molteni, EM Fors. Estradiol receptor-binding protein in head and neck neoplastic and normal tissue. Arch Surg 116:207–210, 1981.
37. N Hamano, N Terada, K Maesako, T Ikeda, S Fukuda, J Wakita, T Yamashita, A Konno. Expression of histamine receptors in nasal epithelial cells and endothelial cells—the effects of sex hormones. Int Arch Allergy Immunol 115:220–227, 1998.
38. N Hamano, N Terada, K Maesako, T Numata, A Konno. Effect of sex hormones on eosinophilic inflammation in nasal mucosa. Allergy Asthma Proc 19:263–269, 1998.
39. B Paulsson, T Gredmark, P Burian, M Bende. Nasal mucosal congestion during the menstrual cycle. J Laryngol Otol 111:337–339, 1997.
40. H Toppozada. The human nasal mucosa in the menopause. J Laryngol Otol 102: 314–318, 1988.
41. RL Mabry. Rhinitis of pregnancy. South Med J 79:965–971, 1986.
42. M Bende, U Hallgårde, C Sjögren, K Uvnäs-Moberg. Nasal congestion during pregnancy. Clin Otolaryngol 14:385–387, 1989.
43. UP Stübner, D Gruber, UE Berger, J Toth, B Marks, J Huber, F Horak. The influence of female sex hormones on nasal reactivity in seasonal allergic rhinitis. Allergy 54:865–871, 1999.
44. A Ginzel, P Illum. Nasal mucocilliary clearance in patients with septal deviation. Rhinology 18:177–181, 1980.
45. CM Rossman, JB Forrest, RE Ruffin, MT Newhouse. Immotile cilia syndrome in persons with and without Kartagener's syndrome. Am Rev Respir Dis 121:1011–1016, 1980.
46. DF Proctor. Transnasal Systemic Medications. Amsterdam: Elsevier, 1985, pp. 101.
47. K Khanvilkar, MD Donovan, DR Flanagan. Drug transfer through mucus. Adv Drug Del Rev 28:173–193, 2001.
48. E Marttin, JC Verhoef, C Cullander, SG Romeijn, JF Nagelkerke, FWHM Merkus. Confocal laser scanning microscopic visualization of the transport of dextrans after nasal administration to rats: effects of absorption enhancers. Pharm Res 14:631–637, 1997.

Copyright © 2003 Marcel Dekker, Inc.

49. C McMartin, LEF Hutchinson, R Hyde, GE Peters. Analysis of structural requirements for the absorption of drugs and macromolecules from the nasal cavity. J Pharm Sci 76:535–540, 1987.
50. V Agarwal, B Mishra. Recent trends in drug delivery systems: intranasal drug delivery. Ind J Exp Biol 37:6–16, 1999.
51. SP Newman, F Morén, SW Clarke. Deposition pattern of nasal sprays in man. Rhinology 26:111–120, 1987.
52. L Illum, SS Davis. Intranasal insulin. Clin Pharmacokinet 12:30–41, 1992.
53. WAJJ Hermens, CWJ Belder, JMWM Merkus, PM Hooymans, J Verhoef, FWHM Merkus. Intranasal administration of estradiol in combination with progesterone to ovariectomized women: a pilot study. Eur J Obstet Gynecol Reprod Biol 43:65–70, 1992.
54. A Adjei, D Sundberg, J Miller, A Chun. Bioavailability of leuprolide acetate following nasal and inhalation delivery to rats and healthy humans. Pharm Res 9:244–249, 1992.
55. A Hoffman, E Ziv. Pharmacokinetic considerations of new insulin formulations and routes of administration. Clin Pharmacokinet 33:285–301, 1997.
56. E Cincinelli, F Savino, I Cagnazzo, P Scorcia, P Galantino. Progesterone administration by nasal spray in menopausal women: comparison between two different spray formulations. Gynecol Endocrinol 6:247–251, 1992.
57. N Eller, CJ Kollenz, G Hitzenberger. A comparative study of pharmacodynamics and bioavailability of 2 different desmopressin nasal sprays. Int J Clin Pharmacol Ther 36:139–145, 1998.
58. A Hussain, T Foster, S Hirai, T Kashihara, R Batenhorst, M Jones. Nasal absorption of propanolol in humans. J Pharm Sci 69:1240, 1980.
59. CJ Johnson, P Olsson, M Bende, T Carlsson, PO Gunnarsson. Absolute bioavailability of nicotine applied to different nasal regions. Eur J Clin Pharmacol 41:585–588, 1991.
60. T Sakane, M Akizuki, Y Taki, S Yamashita, H Sezaki, T Nadai. Direct drug transport from the rat nasal cavity to the cerebrospinal fluid: the relation to the molecular weight of drugs. J Pharm Pharmacol 47:379–384, 1995.
61. Y Wang, R Aun, FLS Tse. Brain uptake of dihydroergotamine after intravenous and nasal administration in the rat. Biopharm Drug Dispos 19:571–575, 1998.
62. T Sakane, S Yamashita, N Yata, H Sezaki. Transnasal delivery of 5-fluorouracil to the brain in the rat. J Drug Target 7:233–240, 1999.
63. AN Fisher, K Brown, SS Davis, GD Parr, DA Smith. The effect of molecular size on the nasal absorption of water-soluble compounds in the albino rat. J Pharm Pharmacol 39:357–362, 1987.
64. A De Ascentüs, R Bettini, G Caponetti, PL Catellani, MT Peracchia, P Santi, P Colombo. Delivery of nasal powders of β-cyclodextrin by insufflation. Pharm Res 13:734–738, 1996.
65. D Corbo, J Liu, YW Chien. Drug absorption through mucosal membranes: effect of mucosal route and penetrant hydrophilicity. Pharm Res 6:848–852, 1989.
66. T Ohwaki, H Ando, S Watanabe, Y Miyake. Effects of dose, pH, and osmolarity on the nasal absorption of secretin in rats. J Pharm Sci 74:550–552, 1985.
67. T Ohwaki, H Ando, F Kakimoto, K Uesugi, S Watanabe, Y Miyake, M Kayano.

Copyright © 2003 Marcel Dekker, Inc.

Effects of dose, pH, and osmolarity on nasal absorption of secretin in rats. II. Histological aspects of the nasal mucosa in relation to the absorption variation due to the effects of pH and osmolarity. J Pharm Sci 76:695–698, 1987.
68. CR Behl, HK Pimplaskar, AP Sileno, J deMeireles, VD Romeo. Effects of physiochemical properties and other factors on systemic nasal drug delivery. Adv Drug Del Rev 29:89–116, 1998.
69. N Shimoda, Y Maitani, Y Machida, T Nagai. Effects of dose, pH and osmolarity on intranasal absorption of recombinant human erythropoietin in rats. Biol Pharm Bull 18:734–739, 1995.
70. P Valensi, P Zirinis, P Nicolas, G Perret, D Sandre-Banon, JR Attali. Effect of insulin concentration on bioavailability during nasal spray administration. Path Biol 44:235–240, 1996.
71. AA Hussain, R Bawarshi-Nassar, CH Huang. Physiochemical consideration in intranasal drug administrations. In: YW Chein, ed. Transnasal Systemic Medications. Amsterdam: Elsevier, 1985, pp. 121–137.
72. AW Proetz. Applied Physiology of the Nose. St. Louis: Annals Publishing Company, 1953.
73. AS Harris, M Ohlin, S Lethagen, IM Nilsson. Effects of concentration and volume on nasal bioavailability and biological response to desmopressin. J Pharm Sci 77: 337–339, 1988.
74. HJM van de Donk, FWHM Merkus. Decreases in ciliary beat frequency due to intranasal administration of propanolol. J Pharm Sci 71:595–596, 1982.
75. IL Bernstein. Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? A cautionary note based on compromised mucocilliary transport. J Allergy Clin Immunol 105:39–44, 2000.
76. G Hillardal. Adverse reaction to locally applied preservatives in nose drops. ORL J Otorhinolaryngol Relat Spec 47:278–279, 1985.
77. H Hallén, P Graf. Benzalkonium chloride in nasal decongestive sprays has a long-lasting adverse effect on the nasal mucosal of healthy volunteers. Clin Exp Allergy 25:401–405, 1995.
78. P Graf, H Hallén. Effect on the nasal mucosa of long-term treatment with oxymetazoline, benzalkonium chloride, and placebo nasal sprays. Laryngoscope 106:605–609, 1996.
79. P Graf, H Hallén, J-E Juto. Benzalkonium chloride in a decongestant nasal spray aggravates rhinitis medicamentosa in healthy volunteers. Clin Exp Allergy 25:395–400, 1995.
80. M Quadir, H Zia, TE Needham. Development and evaluation of nasal formulations of ketorolac. Drug Deliv 7:223–229, 2000.
81. N Griffith, S Howell, DG Mason. Intranasal midazolam for premedication of children undergoing day-case anaesthesia: comparison of two delivery systems with assessment of intra-observer variability. Br J Anaesth 81:865–869, 1998.
82. SF Conley. Comparative trial of acceptability of beclomethasone dipropionate and a new formulation of flunisolide. Ann Allergy 72:829–832, 1994.
83. EO Meltzer, HA Orgel, RK Bush, JR Haltom, J Metzger, BA Moss, DQ Mitchell, ZK Ballas, JM Seltzer, GG Shapiro, JH Van Bavel. Evaluation of symptom relief,

Copyright © 2003 Marcel Dekker, Inc.

nasal airflow, nasal cytology, and acceptability of two formulations of flunisolide nasal spray in patients with perennial allergic rhinitis. Ann Allergy 64:536–540, 1990.
84. S Denyer. Pharmaceutical properties of fluticasone propionate nasal drops: a new formulation. Allergy 54:17–20, 1999.
85. MI Ugwoke, N Verbeke, R Kinget. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol 53:3–22, 2001.
86. E Marttin, JC Verhoef, FWHM Merkus. Efficacy, safety and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs. J Drug Target 6:17–36, 1998.
87. E Marttin, JC Verhoef, F Spies, J van der Meulen, JF Nagelkerke, HK Koerten, FWHM Merkus. The effect of methylated β-cyclodextrins on the tight junctions of the rat nasal respiratory epithelium: electron microscopic and confocal laser scanning microscopic visualization studies. J Control Rel 57:205–213, 1999.
88. K Matsubara, K Abe, T Irie, K Uekema. Improvement of nasal bioavailability of luteinizing hormone-releasing hormone agonist, burserelin, by cyclodextrin derivatives in rats. J Pharm Sci 84:1295–1300, 1995.
89. C Agerholm, L Bastholm, PB Johansen, MH Nielsen, F Elling. Epithelial transport and bioavailability of intranasally administered human growth hormone formulated with the absorption enhancers didecanoyl-L-α-phosphatidylcholine and α-cyclodextrin in rabbits. J Pharm Sci 83:1706–1711, 1994.
90. FWHM Merkus, JC Verhoef, SG Romeijn, NGM Schipper. Absorption enhancing effect of cyclodextrins on intranasally administered insulin in rats. Pharm Res 8: 588–592, 1991.
91. Y Watanabe, Y Matsumoto, K Kawamoto, S Yazawa, M Matsumoto. Enhancing effect of cyclodextrins on nasal absorption of insulin and its duration in rabbits. Chem Pharm Bull 40:3100–3104, 1992.
92. Z Shao, R Krishnamoorthy, A Mitra. Cyclodextrins as nasal absorption promoters of insulin: mechanistic evaluations. Pharm Res 9:1157–1163, 1992.
93. NGM Schipper, SG Romeijn, JC Verhoef, FWHM Merkus. Nasal insulin delivery with dimethyl-β-cyclodextrin as an absorption enhancer in rabbits: powder more effective than liquid formulations. Pharm Res 10:682–686, 1993.
94. NGM Schipper, JC Verhoef, LM De Lannoy, SG Romeijn, JH Brakkee, VM Wiegant, WH Gispen, FWHM Merkus. Nasal administration of an ACTH(4-9) peptide analogue with dimethyl-β-cyclodextrin as an absorption enhancer: pharmacokinetics and dynamics. Br J Pharmacol 110:1334–1340, 1993.
95. NSM Schipper, JC Verhoef, SG Romeijn, FWHM Merkus. Methylated β-cyclodextins are able to improve the nasal absorption of salmon calcitonin. Calcif Tissue Int 56:280–282, 1995.
96. M Machida, K Sano, M Arakawa, M Hayashi, S Awazu. Effects of surfactants and protease inhibitors on nasal absorption of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in rats. Biol Pharm Bull 17:1375–1378, 1994.
97. K Morimoto, H Yamaguchi, Y Iwakura, M Miyazaki, E Nakatani, T Iwamoto, Y Ohashi, Y Nakai. Effects of proteolytic enzyme inhibitors on the nasal absorption of vasopressin and an analogue. Pharm Res 8:1175–1179, 1991.

Copyright © 2003 Marcel Dekker, Inc.

98. K Drejer, A Vaag, K Bech, P Hansen, AR Sørensen, N Mygind. Intranasal administration of insulin with phospholipid as absorption enhancer: pharmacokinetics in normal subjects. Diabet Med 9:335–340, 1992.
99. BJ Aungst, NJ Rogers. Site dependence of absorption-promoting actions of laureth-9, Na salicylate, Na_2EDTA, and aprotinin on rectal, nasal, and buccal insulin delivery. Pharm Res 5:305–308, 1988.
100. S Kagatani, T Shinoda, M Fukui, T Ohmura, S Hasumi, T Sonobe. Enhancement of nasal salmon calcitonin absorption by lauroylcarnitine chloride in rats. Pharm Res 13:739–743, 1996.
101. M Mishima, S Okada, Y Wakita, M Nakano. Promotion of nasal absorption of insulin by glycyrrhetinic acid derivatives. I. J Pharmacobio-Dyn 12:31–36, 1989.
102. C Baglioni, RJ Phipps. Nasal absorption of interferon: enhancement by surfactant agents. J Interferon Res 10:497–504, 1990.
103. MJM Duerloo, WAJJ Hermens, SG Romeyn, JC Verhoef, FWHM Merkus. Absorption enhancement of intranasally administered insulin by sodium taurodihydrofusidate (STDHF) in rabbits and rats. Pharm Res 6:853–856, 1989.
104. K Hosoya, H Kubo, T Akutsu, H Natsume, K Sugibayashi, Y Morimoto. Effect of sodium taurodihydrofusidate on nasal drug delivery: differences in its concentration and penetrant molecular weight. Arch Pharm Res 17:57–59, 1994.
105. A Donnelly, IW Kellaway, G Taylor, M Gibson. Absorption enhancers as tools to determine the route of nasal absorption of peptides. J Drug Target 5:121–127, 1997.
106. L Illum. Bioadhesive formulations for nasal peptide delivery. In: E Mathiowitz, DE Chickering III, C Lehr, eds. Bioadhesive Drug Delivery Systems. New York: Marcel Dekker, 1999, pp. 507–541.
107. KA Janes, P Calvo, MJ Alonso. Polysaccharide colloidal particles as delivery systems for macromolecules. Adv Drug Del Rev 47:83–97, 2001.
108. P Tengamnuay, A Sahamethapat, A Sailasuta, AK Mitra. Chitosans as nasal absorption enhancers of peptides: comparison between free amine chitosans and soluble salts. Int J Pharm 197:53–67, 2000.
109. EA McNeela, D O'Connor, I Jabbal-Gill, L Illum, SS Davis, M Pizza, S Peppoloni, R Rappuoli, KHG Mills. A mucosal vaccine against diphtheria: formulation of cross reacting material (CRM_{197}) of diphtheria toxin with chitosan enhances local and systemic antibody and Th2 responses following nasal delivery. Vaccine 19:1188–1198, 2001.
110. C Sankar, M Rani, AK Srivastava, B Mishra. Chitosan based pentazocine microspheres for intranasal systemic delivery: development and biopharmaceutical evaluation. Pharmazie 56:223–226, 2001.
111. L Illum, NF Farraj, SS Davis. Chitosan as a novel nasal delivery system for peptide drugs. Pharm Res 11:1186–1189, 1994.
112. J Woodley. Bioadhesion new possibilities for drug administration? Clin Pharmacokinet 40:77–84, 2001.
113. R Fernández-Urrusono, P Calvo, C Remuñán-López, JL Vila-Jato, MJ Alonso. Enhancement of nasal absorption of insulin using chitosan nanoparticles. Pharm Res 16:1576–1581, 1999.

Copyright © 2003 Marcel Dekker, Inc.

114. RJ Soane, M Frier, AC Perkins, NS Jones, SS Davis, L Illum. Evaluation of the clearance characteristics of bioadhesive systems in humans. Int J Pharm 178:55–65, 1999.
115. H Critchley, SS Davis, NF Farraj, L Illum. Nasal absorption of desmopressin in rats and sheep. Effect of a bioadhesive microsphere delivery system. J Pharm Pharmacol 46:651–656, 1994.
116. P Edman, E Bjork, L Ryden. Microspheres as a nasal delivery system for peptide drugs. J Control Rel 21:165–172, 1992.
117. MI Ugwoke, E Sam, G Van Den Mooter, N Verbeke, R Kinget. Nasal mucoadhesive delivery systems of the anti-parkinsonian drug, apomorphine: influence of drug-loading on in vitro and in vivo release in rabbits. Int J Pharm 181:125–138, 1999.
118. MI Ugwoke, RU Agu, M Jorissen, P Augustijns, R Sciot, N Verbeke, R Kinget. Nasal toxicological investigations of carbopol 971P formulation of apomorphine: effects on ciliary beat frequency of human nasal primary cell culture and in vivo on rabbit nasal mucosa. Eur J Pharm Sci 9:387–396, 2000.
119. JS Chu, R Chandrasekharan, GL Amidon, ND Weiner, AH Goldberg. Viscometric study of polyacrylic acid systems as mucoadhesive sustained-release gels. Pharm Res 8:1408–1412, 1991.
120. MI Ugwoke, RU Agu, M Jorissen, P Augustijns, R Sciot, N Verbeke, R Kinget. Toxicological investigations of the effects carboxymethylcellulose on ciliary beat frequency of human nasal epithelial cells in primary suspension culture and in vivo of rabbit nasal mucosa. Int J Pharm 205:43–51, 2000.
121. MI Ugwoke, G Kaufmann, N Verbeke, R Kinget. Intranasal bioavailability of apomorphine from carboxymethylcellulose-based drug delivery systems. Int J Pharm 202:125–131, 2000.
122. K Nakamura, Y Maitani, AM Lowman, K Takayama, NA Peppas, T Nagai. Uptake and release of budesonide from mucoadhesive, pH-sensitive copolymers and their application to nasal delivery. J Control Rel 61:329–335, 1999.
123. M Singh, M Briones, DT O'Hagan. A novel bioadhesive intranasal delivery system for inactivated influenza vaccines. J Control Rel 70:267–276, 2001.
124. LE Bromberg. Enhanced nasal retention of hydrophobically modified polyelectrolytes. J Pharm Pharmacol 53:109–114, 2001.
125. K Morimoto, H Katsumata, T Yabuta, K Iwanaga, M Kakemi, Y Tabata, Y Ikada. Evaluation of gelatin microspheres for nasal and intramuscular administrations of salmon calcitonin. Eur J Pharm Sci 13:179–185, 2001.
126. B Brime, MP Ballesteros, P Frutos. Preparation and in vitro characterization of gelatin microspheres containing levodopa for nasal administration. J Microencapsul 17:777–784, 2000.
127. K Aikawa, K Matsumoto, H Uda, S Tanaka, H Shimamura, Y Aramaki, S Tsuchiya. Prolonged release of drug from O/W emulsion and residence in rat nasal cavity. Pharm Dev Technol 3:461–469, 1998.
128. TW Kim, H Chung, IC Kwon, HC Sung, SY Jeong. In vivo gene transfer to the mouse nasal cavity mucosa using a stable cationic lipid emulsion. Mol Cells 10: 142–147, 2000.

Copyright © 2003 Marcel Dekker, Inc.

129. TT Kararli, TE Needham, G Schoenhard, DA Baron, RE Schmidt, B Katz, B Belonio. Enhancement of nasal delivery of a renin inhibitor in the rat using emulsion formulations. Pharm Res 9:1024–1028, 1992.
130. SL Law, KJ Huang, HY Chou. Preparation of desmopressin-containing liposomes for intranasal delivery. J Control Rel 70:375–382, 2001.
131. BH Jung, BC Chung, S Chung, M Lee, C Shim. Prolonged delivery of nicotine in rats via nasal administration of proliposomes. J Control Rel 66:73–79, 2000.
132. D Betbeder, S Spérandio, J Latapie, J de Nadaí, A Etienne, J Zajac, B Frances. Biovector nanoparticles improve antinociceptive efficacy of nasal morphine. Pharm Res 17:743–748, 2000.
133. M Tobío, R Gref, A Sánchez, R Langer, MJ Alonso. Stealth PLA-PEG nanoparticles as protein carriers for nasal administration. Pharm Res 15:270–275, 1998.
134. JE Nally, S Artiushin, AS Sheoran, PJ Burns, B Simon, RM Gilley, J Gibson, S Sullivan, JF Timoney. Induction of mucosal and systemic antibody specific for SeMF3 of *Streptococcus equi* by intranasal vaccination using a sucrose acetate isobutyrate based delivery system. Vaccine 19:492–497, 2001.

Copyright © 2003 Marcel Dekker, Inc.

62

Poly(ethylene oxide)-*b*-Poly(propylene oxide)-*b*-Poly(ethylene oxide)-*g*-Poly(acrylic acid) Copolymers as In Situ Gelling Vehicle for Nasal Delivery

Lev Bromberg
Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A.

I. INTRODUCTION

Copolymers of poly(ethylene oxide) (PEO), poly(propylene oxide) (PPO), and poly(acrylic acid) (PAA) are mucoadhesive and gel at the temperature of human body owing to the formation of micellar aggregates acting as cross-links. The copolymer-drug formulation is injected or sprayed as a liquid into the nasal cavity and quickly gels. The gelation lowers the rate of diffusion and erosion of the polymer and associated drug, thereby enhancing drug retention and bioavailability. The micelles stabilize proteins and allow solubilization of hydrophobic drugs. Several patents and international patent applications on topical drug delivery utilizing the copolymers have been published [1–5].

II. HISTORICAL DEVELOPMENT

Mucoadhesive polymers can enhance local delivery of drugs by adhering to mucosal surfaces present on buccal, gastric, enteric, genitourinary, ophthalmic, pulmonary, and nasal tissues. Most mucoadhesive polymers are unmodified polyelectrolytes that are ionized at physiological pH, thus rapidly swell and dissolve

Copyright © 2003 Marcel Dekker, Inc.

in contact with biological fluids eroding from the site of application. The ability of polyelectrolytes as vehicles to enhance the residence time of the associated drug is then compromised. A variety of formulation approaches have been developed aimed at enhancing the drug residence time and lowering the release rate, while maintaining the mucoadhesive properties of the polyelectrolyte. Typically, a polyelectrolyte is mixed with more hydrophobic polymer to result in a blend with enhanced drug-polymer interactions and higher viscosity. Since administration of highly viscous formulations by a common spray device is difficult, it is preferred that a liquid drug-polymer formulation would gel at the site of administration. Such in situ gelling systems undergo reversible sol-gel transitions in response to temperature, pH, or ion composition of the fluids [6–8].

Formulations based on physical blends are colloidally unstable and tend to either phase-separate or dissociate at physiological pH [9]. Stability of the in situ gelling systems can be enhanced by utilization of a benign copolymer incorporating both a polyelectrolyte segment (which makes the copolymer mucoadhesive) and a hydrophobic segment (which causes the copolymer to aggregate and gel). The copolymers that contain both polyelectrolytes and hydrophobic segments are called hydrophobically modified polyelectrolytes (HMP) and/or polyelectrolyte block-copolymers [9,10]. HMP based on pluronic-modified poly(acrylic acid) (PAA) have been extensively studied as in situ gelling systems [1–5,9–41]. PAA is the industry benchmark for mucoadhesive polymers and is generally recognized as safe in topical pharmaceutical formulations [42–44]. The PAA bonding with benign polymeric surfactants such as the PEO-PPO-PEO block copolymers known under the generic name poloxamers and the trade names Pluronic (BASF) or Synperonic (ICI) results in a thermo-and pH-sensitive, in situ gelling system that has stability absent in a physical blend. Pluronics are the only up-to-date synthetic thermogelling polymers approved by the U.S. Food and Drug Administration as food additives and pharmaceutical ingredients [45]. In situ gelling solutions of Pluronics have been proposed for nasal delivery [46,47]. When administered, formulations based on concentrated solutions of Pluronics undergo a sol-gel transition and the resulting gels have longer residence time in the nasal cavity. Owing to a relatively low molecular weight of the Pluronics, high-polymer concentrations are required for their solutions to gel. Besides, Pluronics per se are not sufficiently mucoadhesive. Hence, the copolymers of PAA and Pluronic (Pluronic-PAA) have been developed that are strongly mucoadhesive and have thermogelling capability at low concentrations.

III. TECHNOLOGY DESCRIPTION AND RESEARCH AND DEVELOPMENT

Covalent bonding between PAA and Pluronic result in a novel polymer with generally unknown regulatory status. However, such copolymer is safe and would

Copyright © 2003 Marcel Dekker, Inc.

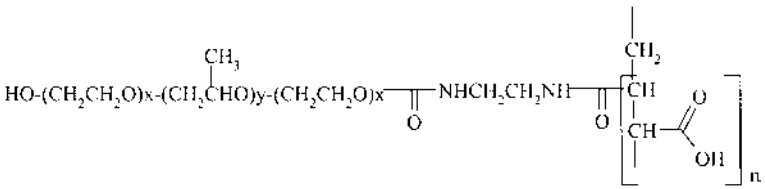


Figure 1 Structure of Pluronic-PAA copolymer obtained by grafting of PEO-PPO-PEO copolymers onto PAA backbone [10,48].

probably have a better regulatory status compared to most other pH-and temperature-sensitive polymers. Hoffman et al. [2,38–41] grafted amino-terminated Pluronic block-copolymers onto PAA backbone (Fig. 1).

Hydrophobic Pluronics with PEO content of only 10–20% that have an appropriate lower critical solution temperature (LCST) were used for grafting onto a relatively long-chain PAA. At temperatures above LCST, interchain associations of Pluronics in these copolymers lead to viscosification of the solution and turbidity, characteristic of phase separation. In vitro release studies with an antiglaucoma drug, timolol maleate, as well as with insulin and cytokines (inflammatory agonists) showed that the gelation of the drug-polymer solution at 34–37°C leads to a significantly prolonged drug release rate due to lower erosion (dissolution) rate of the polymers and drugs from the gels [41]. We introduced graft-copolymers of PAA and Pluronic, whereby PAA and the polyether are linked via the C-C bond [1,3–5,9–37] (Fig. 2).

Aqueous solutions of the resulting Pluronic-PAA copolymers exhibit no macroscopic phase separation, despite the abundance of the micellar aggregates formed above critical micellization concentration and temperature [21,26]. Aggregation in Pluronic-PAA solutions is unrelated to the LCST of the parent Pluronic, so that virtually any Pluronic can be utilized in the copolymer [16,21,35]. By linking two safe polymers, PAA and Pluronic, via C-C bond, no new chemical moiety is introduced into the copolymer.

Gelation in semidilute (0.5–2 wt%) aqueous solutions of the graft-comb Pluronic-PAA copolymers occurs at body temperatures (Fig. 3), providing a convenient in situ gelling vehicle.

Toxicological animal studies have confirmed the nonirritating, benign nature of the Pluronic-PAA formulations with added salts or mannitol as isotonizing agent [1,3,17]. Additionally, the Pluronic-PAA solutions were shown to be mucoadhesive, both in model rheological studies in blends with mucin [10,15,17,24], and in nasal, vaginal, esophageal, and ophthalmic in vivo studies. These solutions are transparent at any temperature and thus are user-friendly [21]. The solutions can be instilled as liquid phases to quickly form thin gel layers on mucous sur-

Copyright © 2003 Marcel Dekker, Inc.

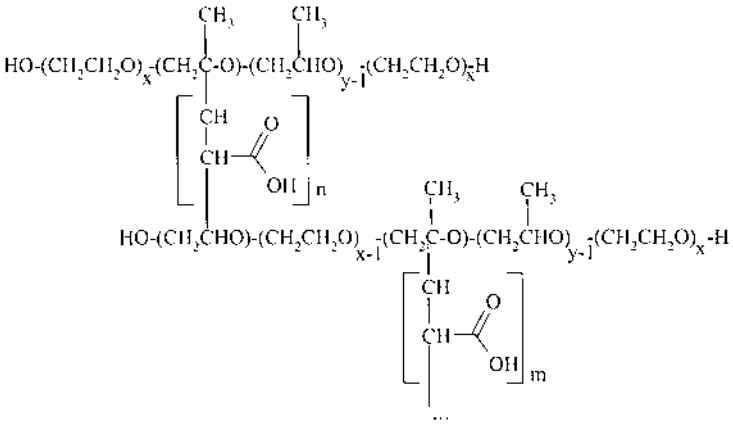


Figure 2 Structure of Pluronic-PAA copolymers obtained by linking of PEO-PPO-PEO Pluronic surfactants with PAA via C-C bond [9,10,17]. The Pluronic-PAA graft-comb copolymers are typically characterized by very high molecular weights (10^5–10^8 Da) and some degree of cross-linking.

faces at the temperatures of the human body. The gelled Pluronic-PAA solutions are extremely shear-sensitive.

A. In Vitro Release Mechanisms

In vitro release studies demonstrated that the mechanisms of release depend upon the nature of the drug-polymer interactions as well as on the size of the drug. Thus, there exist two modes of transport of hydrophobic drugs (steroid hormones) from the gelled Pluronic-PAA systems: the drug that was incorporated into the hydrophobic cores of the micellar aggregates is released very slowly by Fickian diffusion, whereas erosion of the gel by hydrodynamic flow allows for the rapid release of the drug not associated with the aggregates [17,28]. Diffusion of globular proteins in Pluronic-PAA solutions shows profound temperature dependency, with a significant decrease of the diffusion coefficients at body temperature where micellar aggregates form and solution gels. The dense aggregates act as "sieves"; i.e., the protein diffusion can be explained by the protein motion in the interstices between aggregates [33]. In vitro experiments demonstrated that Pluronic-PAA prevents insulin precipitation [32]. Viscosification of the solution lowers the convectional flows and protein diffusion in Pluronic-PAA solutions, thus reducing the frequency of encounters of the protein molecules necessary for aggregation. Furthermore, since Pluronic-PAA is surface-active [20], it occupies the hydrophobic air-water interface [34]. This prevents insulin from aggregating on the

Copyright © 2003 Marcel Dekker, Inc.

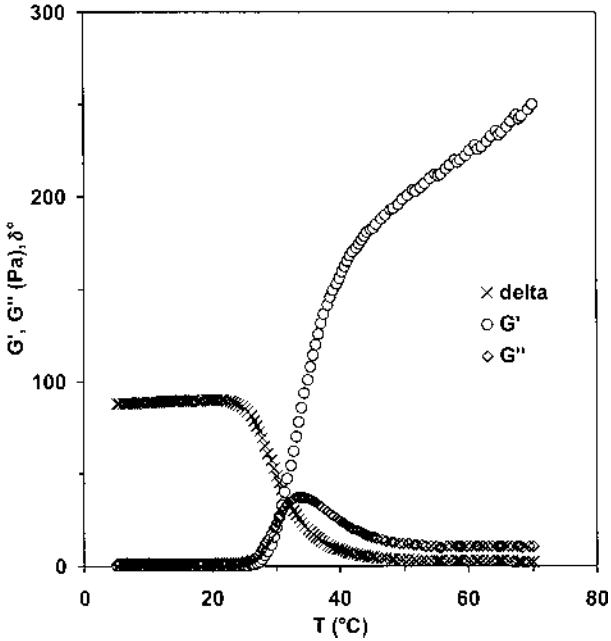


Figure 3 Temperature dependence of rheological parameters of Pluronic-PAA, Pluronic F127, and Pluronic/PAA physical blend solutions. Storage (G′) and loss (G″) moduli and phase angle (δ°) of 2% Pluronic-PAA solution are shown. Oscillatory stress of 60 mPa, frequency of oscillatory shear of 1 Hz, and pH 6.5 are applied. (Reproduced from Ref. [31], with permission from the author.)

interface. The diffusion of flexible chains such as dextrans or nucleic acids in Pluronic-PAA solutions depends on the radius of gyration of the solute and the mean pore size, when the solution is gelled [33].

B. In Vivo Studies

The ability of the Pluronic-PAA solutions to gel has been exploited in in vivo animal studies and in human volunteers [17,31,48]. For instance, administration of the Pluronic-PAA solutions in the nasal cavity of rats leads to the enhancement of the residence time of fluorescent labels (associated with the copolymer) to a 5–8-fold greater extent than lightly cross-linked PAA (Carbopol), and 3–6-fold greater than Pluronic gel [31] (Fig. 4). Pluronic-PAA exerted a significant influence on the plasma glucose level when used as a gelling vehicle for insulin

Copyright © 2003 Marcel Dekker, Inc.

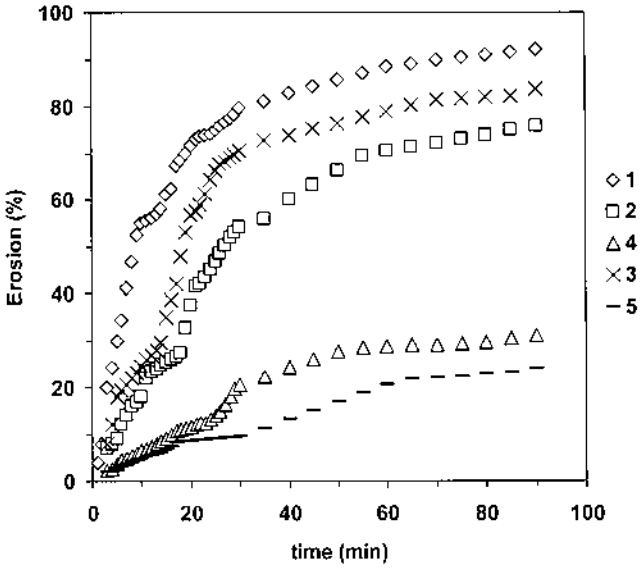


Figure 4 Intranasal clearance profiles for the buffer solution (1), 20 wt% Pluronic F127 (2), 0.4% Carbopol (3), 2% Pluronic-PAA (4), and 2% Pluronic-PAA labeled by covalently attached fluorescein (5). Curves 1–4 are obtained using fluorescence of latex FluoSpheres loaded into corresponding formulation; curve 5 is obtained using fluorescence of the polymer. Error bars are not shown for clarity. Maximum standard deviations were 9%, 18%, 33%, 32%, and 34% for datapoints in curves 1, 2, 3, 4, and 5, respectively. (Reproduced from Ref. [31], with permission from the author.)

(Fig. 5). The effect was comparable to that of a known nasal drug delivery vehicle such as Carbopol formulation.

Since micellization in the Pluronic-PAA solutions greatly enhances the solution capacity for solubilization of a hydrophobic drug [28], the solutions appear to be effective vehicles in administration of steroid hormones and other hydrophobic solutes [17]. The pharmacokinetics of the Pluronic-PAA-solubilized steroid hormones estradiol and testosterone in ovine vaginal and rabbit nasal delivery demonstrated that the thermogelling formulations enhanced bioavailability and prolonged the effect of the hormones [3].

As Pluronic-PAA stabilizes proteins and peptides in the in situ gelling formulations [32], bioactive peptides such as luteinizing hormone releasing hormone (LHRH) and its synthetic nonapeptide agonist analogs leuprolide and deslorelin

Copyright © 2003 Marcel Dekker, Inc.

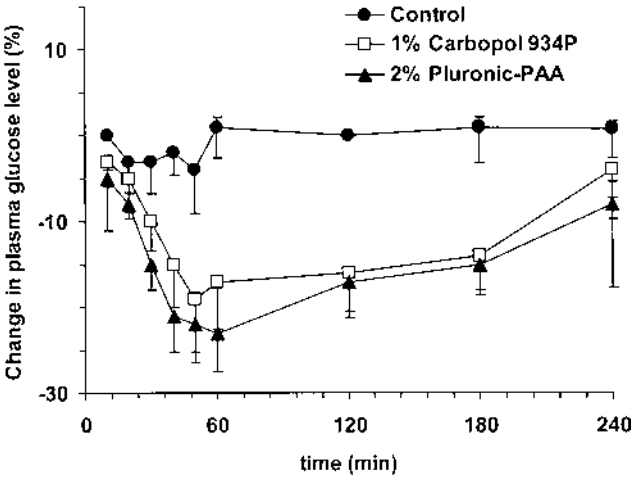


Figure 5 Change in plasma glucose level (±SD) after intranasal administration of human insulin in male Sprague-Dawley rats. The insulin solutions (pH 7.4 throughout) in physiological saline (control), 2 wt% Pluronic-PAA, or 1 wt% Carbopol 934P solution were injected by volume, 20–25 μL, in a rat nostril, to give a dose of 5 IU/kg. The blood samples were withdrawn from the arteria carotis, centrifuged, and the plasma was assayed for glucose content. The total decrease in the plasma glucose level was calculated as a relative difference in area under the curve in the control and given experiment, as described elsewhere [49].

were tested in vaginal and nasal delivery in animal models [3]. Administration of each peptide formulation caused an increase in the LHRH levels.

IV. FUTURE DIRECTIONS

Future directions in the development of Pluronic-PAA copolymers will involve the appearance of permanently cross-linked microgel particles that can be highly loaded with proteinaceous drugs and anticancer compounds and yet are temperature- and pH-sensitive [50]. The microgel particles can be less irritating to the ciliary action of the nasal cavity than solutions in chronic applications of the nasal dosage forms. Further on, we expect the advent of biodegradable HMP that can carry drugs that are cell- or receptor-specific. Such HMP will gel on the mucosal surfaces and change the initial stages of endocytosis, thus affecting the uptake of macromolecular drugs [51].

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. L Bromberg, EC Lupton, ME Schiller, MJ Timm, G McKinney. Responsive polymer networks and methods of their use. US patent 5,939,485, 1999.
2. AS Hoffman, G Chen. Block and graft copolymers and methods related thereto. Int patent appl WO 95/24430, 1995.
3. ES Ron, L Bromberg, M Orkisz, M Kearney, S Luczak, MJ Timm, SJ Wrobel. Compositions for pharmaceutical applications. Int patent appl WO 98/06438, 1998.
4. ES Ron, BJ Hand, L Bromberg, M Kearney, ME Schiller, PM Ahearn, S Luczak, THE Mendum. Compositions for cosmetic applications. Int patent appl WO 98/50005, 1998.
5. ES Ron, LE Bromberg, M Temchenko. End modified thermal responsive hydrogels. UA patent 6,316,011, 2001.
6. KJ Himmelstein, CL Baustian. Reversible gel-forming composition for sustained delivery of bio-affecting substances, and method of use. US patent 5,599,534, 1997.
7. TX Viegas, LE Reeve, RS Levinson. Body cavity drug delivery with thermoreversible gels containing polyoxyalkylene copolymers. US patent 5,292,516, 1994.
8. R Joshi, DH Robinson, KJ Himmelstein. In vitro properties of an in situ forming gel for the parenteral delivery of macromolecular drugs, Pharm Dev Technol 4:515–522, 1999.
9. L Bromberg. Hydrophobically modified polyelectrolytes and polyelectrolyte block-copolymers. In: HS Nalwa, ed. Handbook of Surfaces and Interfaces of Materials. Vol 4. New York: Academic Press, 2001, Chapter 7.
10. L Bromberg. Biomedical applications of hydrophobically modified polyelectrolytes and polyelectrolyte block-copolymers. In: S Tripathy, J Kumar, HS Nalwa, eds. Handbook of Polyelectrolytes and Their Applications. American Scientific Publishers, Stevenson Ranch, CA, 2002, Vol. 1, Chaper 51.
11. LE Bromberg, THE Mendum, M Orkisz, ES Ron, EC Lupton. Applications of poly(oxyethylene-*b*-oxypropylene-*b*-oxyethylene)-*g*-poly(acrylic acid) polymers (Smart Hydrogel) in drug delivery. Proc Polym Mater Sci Eng 76:273–275, 1997.
12. MJ Orkisz, L Bromberg, R Pike, EC Lupton, ES Ron. Rheological properties of reverse thermogelling poly(acrylic acid)-*g*-poly(oxyethylene-*b*-oxypropylene-*b*-oxyethylene) polymers (Smart Hydrogel). Proc Polym Mater Sci Eng 76:276–277, 1997.
13. L Bromberg, M Orkisz, E Roos, ES Ron, M Schiller. Interpenetrating networks of Poloxamer copolymers and poly(acrylic acid) as vehicles in controlled drug delivery. J Control Rel 48:305–308, 1997.
14. LE Bromberg, THE Mendum, MJ Orkisz, EC Lupton, ES Ron. Polyoxyethylene-*b*-polyoxypropylene-*b*-polyoxyethylene-*g*-poly(acrylic acid) polymers (Smart Hydrogel) as a carrier in controlled delivery of proteins and peptides. Polym Prep 38: 602–603, 1997.
15. LE Bromberg, MJ Orkisz, ES Ron. Bioadhesive properties of polyoxyethylene-*b*-polyoxypropylene-*b*-polyoxyethylene-*g*-poly(acrylic acid) polymers (Smart Hydrogel). Polym Prep 38:626–627, 1997.
16. L Bromberg. A novel family of thermogelling materials via C-C bonding between

Copyright © 2003 Marcel Dekker, Inc.

poly(acrylic acid) and poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide). J Phys Chem B 102:1956–1963, 1998.
17. LE Bromberg, ES Ron. Protein and peptide release from temperature-responsive gels and thermogelling polymer matrices. Adv Drug Del Rev 31:197–221, 1998.
18. LE Bromberg, MG Goldfeld. Self-assembly in aqueous solutions of hydrophobically modified poly(acrylic acid). Polym Prep 39:681–682, 1998.
19. L Bromberg. Scaling of rheological properties of hydrogels from associating polymers. Macromolecules 31:6148–6156, 1998.
20. L Bromberg. Self-assembly in aqueous solutions of polyether-modified poly(acrylic acid). Langmuir 14:5806–5812, 1998.
21. L Bromberg. Polyether-modified poly(acrylic acid): synthesis and properties. Ind Eng Chem Res 37:4267–4274, 1998.
22. L Bromberg. Properties of aqueous solutions and gels of poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide)-*g*-poly(acrylic acid). J Phys Chem B 102:10736–10744, 1998.
23. L Bromberg, L Salvati. Bioactive surfaces via immobilization of self-assembling polymers onto hydrophobic materials. Bioconjug Chem 10:678–686, 1999.
24. LE Bromberg. Interactions between hydrophobically modified polyelectrolytes and mucin. Polym Prep 40:616–617, 1999.
25. LE Bromberg, DP Barr. Aggregation phenomena in aqueous solutions of hydrophobically modified polyelectrolytes: a probe solubilization study. Macromolecules 32: 3649–3657, 1999.
26. PDT Huibers, LE Bromberg, BH Robinson, TA Hatton. Reversible gelation in semidilute aqueous solutions of associative polymers: a small-angle neutron scattering study. Macromolecules 32:4889–4894, 1999.
27. L Bromberg, E Magner. Release of hydrophobic compounds from micellar solutions of hydrophobically modified polyelectrolytes. Langmuir 15:6792–6798, 1999.
28. L Bromberg, M Temchenko. Loading of hydrophobic compounds into micellar solutions of hydrophobically modified polyelectrolytes. Langmuir 15:8627–8632, 1999.
29. LE Bromberg, M Temchenko, RH Colby. Interactions among hydrophobically modified polyelectrolytes and surfactants of the same charge. Langmuir 16:2609–2614, 2000.
30. N Plucktaveesak, LE Bromberg, RH Colby. Effect of surfactants on gelation threshold temperature in aqueous solutions of hydrophobically modified polyelectrolyte. Proc. XIIIth International Congress on Rheology, Cambridge, UK. Vol. 3. 2000, pp. 307–309.
31. L Bromberg. Enhanced nasal retention of hydrophobically modified polyelectrolytes. J Pharm Pharmacol 53:109–114, 2001.
32. L Bromberg. Interactions among proteins and hydrophobically modified polyelectrolytes. J Pharm Pharmacol 53:541–547, 2001.
33. AK Ho, LE Bromberg, AJ O'Connor, JM Perera, GW Stevens, TA Hatton. Solute diffusion in solutions of associative polymers. Langmuir 17:3538–3544, 2001.
34. RH Colby, N Plucktaveesak, L Bromberg. Critical incorporation concentration of surfactants added to micellar solutions of hydrophobically modified polyelectrolytes of the same charge. Langmuir 17:2937–2941, 2001.
35. L Bromberg. Synthesis and self-assembly of poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide)-*g*-poly(acrylic acid) gels. Ind Eng Chem Res 40: 2437–2444, 2001.

Copyright © 2003 Marcel Dekker, Inc.

36. L Olivieri, M Seiller, L Bromberg, E Ron, P Couvreur, J-L Grossiord. Study of the breakup under shear of a new thermally reversible W/O/W multiple emulsion. Pharm Res 18:689–693, 2001.
37. AK Ho, LE Bromberg, PDT Huibers, AJ O'Connor, JM Perera, GW Stevens, TA Hatton. Hydrophobic domains in thermogelling solutions of polyether-modified poly(acrylic acid). Langmuir, 18:3005–3013, 2002.
38. AS Hoffman, GH Chen, SY Kaang, ZL Ding, K Randeri, B Kabra. Novel bioadhesive, pH- and temperature-sensitive graft copolymers for prolonged mucosal drug delivery. In: N Ogata, SW Kim, J Feijen, T Okano, eds. Advanced Biomaterials in Biomedical Engineering and Drug Delivery Systems. Tokyo: Springer, 1996, pp. 62–66.
39. AS Hoffman, G Chen, X Wu, Z Ding, B Kabra, K Randeri, M Schiller, E Ron, NA Peppas, C Brazel. Graft copolymers of PEO-PPO-PEO triblock polyethers on bioadhesive polymer backbones: synthesis and properties. Polym Prep 38:524–525, 1997.
40. G Chen, AS Hoffman, B Kabra, K Randeri. Temperature-induced gelation Pluronic-g-poly(acrylic acid) graft copolymers for prolonged drug delivery to the eye. In: M Harris, S Zalipsky, eds. Poly(ethylene glycol) Chemistry and Biological Applications. ACS Symposium Series 680. Washington, DC: American Chemical Society. 1997, pp. 441–457. Chapter 27.
41. AS Hoffman, G Chen, X Wu, Z Ding, JE Matsuura, WR Gombotz, Stimuli-responsive polymers grafted onto polyacrylic acid and chitosan backbones as bioadhesive carriers for mucosal drug delivery. In: RM Ottenbrite, ed. Frontiers in Biomedical Polymer Applications. Vol. 2. Lancaster, PA: Technomic Publishing Co., 1999, pp. 17–29.
42. Carbopol. The Proven Polymers in Pharmaceuticals. Bulletin 14, Cleveland, OH: BF Goodrich Specialty Chemicals, 1994.
43. JR Robinson, MA Longer, M Veillard. Bioadhesive polymers for controlled drug delivery. Ann NY Acad Sci 507:307–314, 1987.
44. JW Lee, JH Park, JR Robinson. Bioadhesive-based dosage forms: the next generation. J Pharm Sci 89:850–866, 2000.
45. BASF Performance Chemicals. FDA and EPA status. North Mount Olive, NJ: BASF Corporation, 1993.
46. L Illum. Bioadhesive formulations for nasal peptide delivery. In: E Mathiowitz, DE Chickering, CM Lehr, eds. Bioadhesive Drug Delivery Systems. New York: Marcel Dekker, 2000, pp. 507–562.
47. M Hinchcliffe, L Illum. Intranasal insulin delivery and therapy. Adv Drug Del Rev 35:199–234, 1999.
48. AM Potts, CG Wilson, HNE Stevens, DJ Dobrozsi, N Washington, M Frier, AC Perkins. Oesophageal bandaging: a new opportunity for thermosetting polymers. STP Pharma Sci 4:293–301, 2000.
49. S Hirai, T Yashiki, T Matsuzawa, H Mima. Effect of surfactants on the nasal absorption of insulin in rats. Int J Pharm 9:165–172, 1981.
50. L Bromberg, M Temchenko, TA Hatton. Dually responsive microgels from polyether-modified poly(acrylic acid): swelling and drug loading. Langmuir, 18:4944–4952, 2002.
51. DA Edwards, KJ Gooch, I Zhang, GH McKinley, R Langer. The nucleation of receptor-mediated endocytosis. Proc Natl Acad Sci USA 93:1786–1791, 1996.

Copyright © 2003 Marcel Dekker, Inc.

63

Intravaginal Drug Delivery Technologies

A. David Woolfson
Queen's University Belfast, Belfast, Northern Ireland

I. INTRODUCTION

For thousands of years, women have been administering a wide range of substances to the vagina, primarily for contraception or for the treatment of infection. The Kahun Papyrus, an ancient Egyptian treatise on gynecology, mentions such contraceptive methods as the use of a vaginal suppository containing crocodile dung mixed with honey and sodium carbonate. In the Papyrus of Ebers, another ancient Egyptian document on medicine, the recommended method was to insert into the vagina *Acacia* tips containing gum arabic, which, when dissolved in water, liberated lactic acid. This latter preparation is not dissimilar in concept to modern-day intravaginal administration of lactic acid pessaries to restore or maintain the natural, slightly acidic pH of the vagina. More alarmingly, in the nineteenth century, abortion, suicide, and homicide attempts using vaginally administered arsenic and other poisons were not uncommon. Thus, it has long been realized that exogenous chemicals, when administered intravaginally, could find their way into the systemic circulation. However, this belief was not formalized until the publication of the seminal study by David Macht [1] in 1918, which described the absorption of alkaloids, inorganic salts, esters and antiseptics through the vagina, thus demonstrating for the first time the potential for systemic drug delivery via this route.

Copyright © 2003 Marcel Dekker, Inc.

II. INFLUENCE OF VAGINAL ANATOMY AND PHYSIOLOGY ON DRUG DELIVERY

Anatomical and physiological considerations have a direct influence on the design of intravaginal drug delivery systems. The functions of the human vagina, a portion of the female reproductive system, are connected with conception and birth, and its physiology changes with the female life cycle, in addition to variations occurring during the monthly cycle [2,3]. From the drug delivery viewpoint, therefore, the vagina is a potential space that contains a nonconstant environment. Thus, the design of intravaginal drug delivery systems must take account of the anatomy and physiology of the vagina.

The vagina is a highly expandable, slightly S-shaped fibromuscular collapsible tube situated between the rectum, which lies posterior to it, and the urethra and bladder, which lie anterior to it (Fig. 1). It extends from the lower part of the uterine cervix to the external part of the vulva known as the labia minor [4]. The vault of the vagina is divided into four areas relative to the cervix [5]. These are the posterior fornix, which is capacious, the anterior fornix, which is shallow, and two lateral fornices. The anterior wall of the vagina averages 6–7 cm in length, whereas the posterior wall is slightly longer (approximately 7.5–8.5 cm) owing to the intrusion of the cervix below the vault.

The walls of the vagina are composed of four distinctive layers: the stratified mucosa, submucosa, muscularis, and the tunica adventitia [6]. The stratified

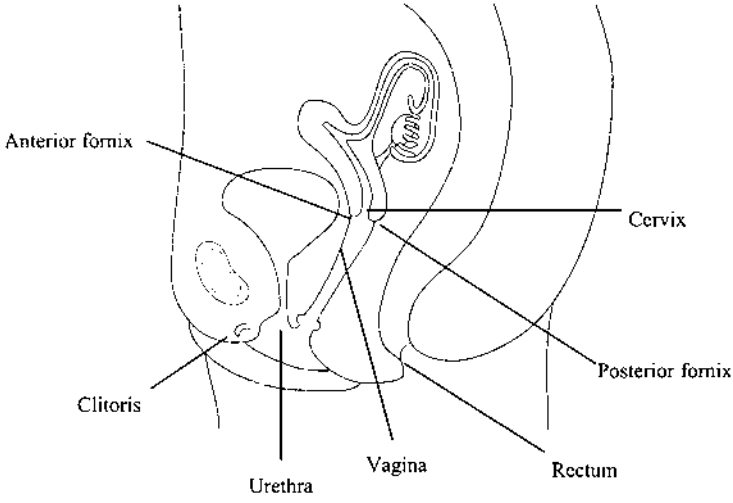


Figure 1 Vaginal anatomy in relation to drug delivery.

Copyright © 2003 Marcel Dekker, Inc.

mucosa, which offers the main barrier to drug absorption, consists of an epithelium and an underlying lamina propria, with the thickness of the epithelium varying by 200–300 μm as a result of changes in estrogen levels during the menstrual cycle. Therefore, the degree of estrogenization of vaginal epithelium has important consequences for drug permeation through the tissue.

The cellular structure of vaginal epithelium consists of five distinct cytological layers: the basal, parabasal, intermediate, transitional, and superficial layers [7]. The basal cells, typically cuboidal in shape and characterized by the presence of microvilli on the surface of the cell membrane [8], are responsible for the continuous production of squamous cells. Parabasal cells are polygonal in shape and differ slightly from the basal cells in having a substantially greater amount of surface microvilli. The cells of the intermediate layer are of the largest cell type and also exhibit microvilli. The transitional cells that follow may show noticeable signs of involution characterized by the reduction of microvilli and intercellular junctions [8]. The superficial layer, as the name suggests, are the cells of the outermost layer, squamous in shape and normally devoid of keratin [9]. These cells store considerable amounts of glycogen, which is released into the vaginal lumen when the surface cells are exfoliated [10].

All layers of the epithelium consist of living cells that renew continuously as they are stimulated by hormonal action and intracellular communication. The constant loss and renewal of cells is characteristic of epithelial membranes. Epithelial cells are very closely packed and are joined together by junctional complexes [11]. Thus, there is no room for blood vessels between adjacent epithelial cells. The epithelium must therefore receive nourishment from the underlying connective tissue, which has large intercellular spaces that can accommodate blood vessels and nerves. Epithelial membranes are attached to the underlying connective tissue by the basement lamina, consisting primarily of proteins and polysaccharides.

Vaginal epithelium is in constant contact with vaginal fluid, formed primarily from transudate that passes through the vaginal wall from the blood vessels. It is mixed with vulval secretions from sebaceous and sweat glands, with minor contributions from Bartholin's and Skene's glands [4]. Vaginal fluid may also contain several enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyketones, and aromatic compounds [12].

Vaginal fluid is normally mixed with cervical mucus and sloughed cells from the vaginal epithelia to the extent that this mucus, produced by glandular units within the cervical canal, is the major component of the fluid. The amount, composition, and physical characteristics of cervical mucus change with the menstrual cycle [13], making its production estrogen-dependent. At the time of ovulation, the amount of cervical secretions further increases, resulting in an increase in the overall volume of vaginal fluid. Consequently, there is an increase in fibrosity, pH, and mucin content and a decrease in the viscosity, cellularity, and

Copyright © 2003 Marcel Dekker, Inc.

albumin concentration [12], with potential effects on drug delivery. Since vaginal fluid is aqueous in nature, it follows that any drug intended for systemic absorption via the vaginal epithelium will require a degree of aqueous solubility.

For drugs that have ionizable functional groups, vaginal pH, in particular, may exert a significant effect on absorption. The vaginal fluid in healthy mature women has a typical pH of between 4 and 5 [5]. The pH value is maintained by the commensal microorganism *Lactobacillus acidophilus*, which produces lactic acid from glycogen contained in the sloughed mature cells of the vaginal mucosa. The acidic nature of the vaginal fluid is important since it offers natural resistance to the colonization of pyrogenic organisms.

Normally, vaginal pH is low in infancy and gradually increases as the concentration of maternal hormones in the infant's body recedes, reaching a pH of 7 where it remains until puberty [13]. The pH of vaginal fluid in the adult rises during menstruation, but it may also increase after periods of frequent acts of coitus as both vaginal transudate, formed during coitus, and ejaculate are alkaline. Physiologically, the anterior fornix of the vagina has the lowest pH, which gradually rises toward the vestibule [2]. Intravaginal pH may also be affected by the presence of cervical mucus, which has a pH in the range 6.5–9 [14], and by the amount of lubricating vaginal secretions. These changes could influence the release profile from intravaginal drug delivery devices by, for example, altering the ratio of charged to uncharged (lipophilic) species of a weakly basic drug, and thus its solubility in vaginal fluid, together with its permeability through the predominantly lipophilic epithelial barrier.

Drug transport across vaginal epithelium may also be affected by enzymatic activity associated with vaginal fluid. For example, enzymatic degradation of polypeptides may lead to low vaginal absorption of these drugs [15]. The basal layer of the vaginal epithelium has a high activity of enzymes found in the citric acid cycle, in fatty acid metabolism, and in 17-ketosteroidogenesis, e.g., succinic dehydrogenase, diaphorase, acid phosphatase, β-glucuronidase, and phosphoamidase [16]. The outer cell layers of the vagina contain β-glucuronidase, acid phosphatase, and smaller quantities of α-naphthylesterase, diaphorase, phosphoamidase, and succinic dehydrogenase. Basal cell layers contain β-glucuronidase, succinic dehydrogenase, diaphorase, small amounts of acid phosphatase, and α-naphthylesterase. Levels of alkaline phosphatase, lactate dehydrogenase, aminopeptidase, and esterase activity are all high in the follicular phase of the menstrual cycle, but fall immediately prior to ovulation [16]. The presence of infective diseases can, of course, affect the levels and types of enzymes found in vaginal fluid [17].

Vaginal epithelium has a rich blood supply originating primarily from the internal iliac artery but, in some cases, may come from the first part of the uterine artery [9]. One aspect of the vascularity of vaginal tissue that has recently attracted attention is the concept of a "first-uterine-pass effect" or direct preferential

Copyright © 2003 Marcel Dekker, Inc.

vagina-to-uterus transport. Evidence of higher-than-expected uterine tissue concentrations after vaginal administration of progesterone [18] has been advanced as one possible consequence of this effect. A "countercurrent" flow of absorbed permeant between venous and arterial systems supplying the vagina has been postulated as a possible mechanism for this event. It has been suggested that the first-uterine-pass effect may allow targeted drug delivery to the uterus via the vaginal route, thereby maximizing the desired effects while minimizing the potential for adverse systemic effects. However, the concept remains unproven and may engender further controversy.

The vaginal environment is a dynamic and closely interrelated mix of facultative and obligate anaerobic microbes, mainly *Lactobacillus*, *Bacteroides*, and *Staphylococcus* species, with new strains constantly being introduced [19]. These microorganisms possess enzymes that enable them to survive and replicate under a given vaginal environment. It is well established that only those microorganisms that can replicate and compete for nutrients in the vagina can become established as part of the natural vaginal flora [3]. Medication has been found to have a direct influence on the vaginal microflora. The selective eradication of certain microorganisms by administration of antibiotics may result in the colonization of the vagina by opportunistic pathogens. Donders and co-workers [20] investigated the effects of phenoxymethylpenicillin on normal vaginal flora in six subjects. Gram-negative strains developed in four of the six women and, in one of the subjects, *Lactobacillus* species had disappeared completely, to be replaced by *Escherichia coli*.

Several research groups have investigated the possible effects of intravaginal drug delivery devices on the normal vaginal microflora [21,22]. For example, intrauterine devices (IUD) have been known to cause local mechanical irritation of the vagina, thus resulting in an increased number of leukocytes and increased mucus secretion at the site of irritation. As a consequence of this, vaginal pH increases, favoring the proliferation of nonacidophilic pathogens [3]. A higher prevalence of anaerobes in IUD users compared with non-IUD users has been reported [23]. In contrast, however, other studies found no significant changes in vaginal flora between users and nonusers of contraceptive elastomeric intravaginal rings [24,25].

III. INTRAVAGINAL DRUG ABSORPTION

Systemic drug absorption across the vaginal epithelium membrane involves drug release from the delivery system, drug dissolution in vaginal fluid, and membrane penetration. Local intravaginal drug treatment follows drug release, dissolution, and delivery throughout the vaginal space. The significant absorption capability of the vagina for exogenous substances, including drugs, is now well recognized.

Copyright © 2003 Marcel Dekker, Inc.

Originally regarded as relatively passive and impermeable to foreign agents, the intravaginal absorption of numerous compounds has now been noted. The emphasis in human clinical trials has been primarily on the systemic delivery of contraceptives [26] and, more recently, on estrogenic and progestogenic compounds for hormone replacement therapy [27]. Currently, there is substantial interest in the intravaginal delivery of therapeutic peptides and proteins [15].

A significant advantage of intravaginal drug delivery is that the route avoids hepatic first-pass metabolism. Thus, for example, intravaginal delivery of estrogenic compounds, which are subject to extensive first-pass metabolism, requires a significantly lower dose than the oral route to achieve the required serum concentration of circulating steroid.

The absorption of drugs or other exogenous substances from the vagina depends on the condition of the epithelial membrane, on the nature of the delivery system, and on physicochemical factors relating to the penetrant, including molecular weight and size, lipophilicity, and ionization state. The local pharmacological action of the drug, thickness of the vaginal wall, presence of cervical mucus, and presence of specific cytoplasmic receptors may also be important. Drug absorption is also modified by changes in the thickness of the vaginal wall influenced by the ovarian cycle or by pregnancy and by postmenopausal changes in the vaginal epithelium and intravaginal pH.

The pathways for drug diffusion across vaginal epithelium are essentially similar to other epithelial tissues [15] and are well represented by the "fluid mosaic model" as a lipid continuum interspersed with aqueous pores, the latter forming an aqueous "shunt" route [28]. The lipid continuum predominates in vaginal drug absorption.

The permeability coefficient of a drug across a vaginal epithelial barrier membrane may be considered as the product of the amount of drug penetrating the membrane per unit time per unit area drug (flux) and the membrane thickness, divided by the drug concentration in the delivery vehicle. For drugs with a high vaginal membrane permeability coefficient, absorption is mainly controlled by permeability across the hydrodynamic diffusion layer formed by vaginal fluid sandwiched between the vaginal epithelial membrane and the delivery device [29]. For drugs with a low vaginal membrane permeability, vaginal absorption is mainly controlled by permeability across the vaginal epithelium [29]. Consequently, in vaginal drug delivery, for systemic drug absorption to occur, the penetrant substance must have sufficient lipophilicity to diffuse through the lipid continuum of the membrane, but also require some degree of aqueous solubility to ensure dissolution in vaginal fluid. This is sometimes a difficult compromise to achieve.

The sequence of events that occurs in intravaginal drug delivery depends, in part, on the nature of the delivery system that is employed, i.e., whether it is solid or semisolid, swellable or erodible, soluble or insoluble, immediate or

Copyright © 2003 Marcel Dekker, Inc.

controlled release. For the purposes of illustration, Flynn and co-workers [30] have described the sequence of events that occur when a solid polymeric reservoir device is used as the delivery system for a hydrophobic drug, such as a steroidal hormone. The drug is initially present as a homogeneous distribution of fine particles within the core of the device, with a small proportion in solution within the polymer system. Drug in solution diffuses through the polymeric sheath, followed by partitioning and diffusion through the vaginal fluid forming the hydrodynamic layer sandwiched between the device and the vaginal wall. The drug then passively diffuses along a concentration gradient, primarily through the lipid continuum of vaginal mucosal epithelium (the transcellular route). In practice, the concentration gradient established with a matrix system is actually a series of such gradients, comprising that between the device and depletion zone boundaries, the gradient across the hydrodynamic layer and that across the epithelial membrane, between the mucosal and serosal sides [30].

The bioavailability of an intravaginally administered drug can be modified by the use of chemical penetration enhancers. These typically act on epithelial tight junctions to provide an alternative intercellular penetration route that may be particularly significant in the vaginal absorption of higher-molecular-weight species such as therapeutic peptides and proteins. The overall permeability of vaginal epithelium to penetrant species is greater than the rectal, buccal, or transdermal routes, but less than the nasal and pulmonary routes [31].

IV. DESIGNING AN INTRAVAGINAL DRUG DELIVERY SYSTEM: KEY CONSIDERATIONS

A wide range of delivery systems are applicable to intravaginal drug delivery, very few of which are specifically designed for the vaginal route. General delivery platforms that may be used intravaginally include creams, foams, pessaries, gels, tablets, and particulate systems. Some of these incorporate the use of one or more mucoadhesive polymeric components [32,33]. The best examples of specifically designed intravaginal delivery systems generally involve solid polymeric systems, usually either elastomers [34] or hydrogels. The choice of optimum delivery system for the intravaginal route depends on a consideration of the following factors:

- The choice between local or systemic delivery may determine, for example, the use of a traditional dosage form, such as a semisolid cream or gel, or a system that promotes increased intravaginal residence, with an increased possibility of absorption across vaginal epithelium.
- Site-specific application may be preferable or it may be required that the drug is distributed rapidly throughout the vaginal space. The latter ap-

Copyright © 2003 Marcel Dekker, Inc.

proach may be best suited to, for example, intravaginal administration of an antimicrobial agent. Site-specific delivery will require the use of a self-locating system, typically a mucoadhesive formulation, although an intravaginal ring, owing to its elastomeric nature, will remain located high in the vaginal space. Conversely, for rapid distribution throughout the space, semisolid or fast-dissolving solid systems will be required. For semisolids, flow properties and viscoelastic character will be critical determinants of their ability to spread rapidly from their point of application.

- Intravaginal drug release may be required to be immediate or modified (sustained or controlled release). Drug release by the intravaginal route is most commonly immediate but a viscoelastic semisolid can be designed to offer some increase in duration of delivery, as can solid hydrogels or intravaginal tablets. For controlled, zero-order release sustained over prolonged periods (days, extending to months), solid polymeric systems may be most suitable, provided they are compatible with the physicochemical nature of the drug to be delivered. Intravaginal applications of controlled release relate to systemic drug delivery applications, typically for potent drugs such as steroid sex hormones and, perhaps, peptides or peptidomimetic agents.
- For systemic drug delivery by the intravaginal route, the physicochemical and pharmacological nature of the penetrant are of paramount importance. The drug to be delivered should be considered in relation to its polarity and partition characteristics, molecular weight, and size, with respect to epithelial penetration, release into vaginal fluid, and performance in either water-based or more hydrophobic delivery systems.
- Vaginal delivery may not be universally acceptable in all cultures, and within cultures the preference for systems that can be self-inserted and removed, or considerations relating to leakage, will vary considerably.
- From an industrial perspective, a cost-benefit analysis is an important factor in deciding upon the choice of delivery system. Capital costs, for example, are considerably higher for specifically designed intravaginal systems than for those capable of manufacture on generic equipment, such as semisolids and intravaginal tablets. These costs must be considered in relation to the commercial value of the active component(s) and the likely benefits in relation to the disease state.

V. INTRAVAGINAL DRUG DELIVERY TECHNOLOGIES

Intravaginal drug delivery systems can be thought as being adapted from semisolid topical systems (usually by design of a vaginal applicator device) or de-

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Intravaginal Drug Delivery Technologies

Delivery platform	Physicochemical aspects
Gels/hydrogels	Rapid drug release from gels
	Most suitable for relatively polar drugs
Tablets	Unlike oral solid dosage forms, limited applications for controlled release—most suitable for immediate-release applications
Pessaries/ suppositories	Rapid drug release
	Can accommodate drugs in solution or suspension
Microspheres	Controlled release possible via matrix, reservoir, swelling, or erodible mechanisms
	Bioadhesive polymers may improve retention
	May enhance intravaginal drug distribution
	May offer protection for labile drugs
Intravaginal rings	Presently limited to highly lipophilic drugs, such as steroids
	Processing temperature not suitable for thermolabile actives
	Variety of release profiles, including zero-order release possible through alteration of ring design

signed specifically for intravaginal use. Existing delivery platforms are summarized in Table 1. Intravaginal drug delivery may be intended for a local effect, such as barrier contraceptive methods, the prevention/treatment of infection, or estronization of vaginal epithelium. It may also be intended to provide controlled, sustained systemic delivery of a range of possible therapeutic agents, including steroid sex hormones for contraception or estrogen/hormone replacement therapy [35]. One exciting area for development is the use of the vaginal route for nonparenteral delivery of peptide and protein drugs, with the assistance of appropriate penetration enhancement strategies [36].

Conventional solutions, semisolids (ointments, creams, and some gels), tablets, and pessaries all suffer from problems of retention and spreadability when used intravaginally. Semisolids, in particular, are perceived as messy in use and prone to leakage. Conventional systems often do not offer sufficient flexibility in design, with respect to controlling the drug release rate and sustaining release over periods extending from days to, perhaps, months. Thus, specific intravaginal drug delivery designs are continuing to evolve. These are largely based on nonspecific mucoadhesive hydrogel systems, cytoadhesive targeted systems, solid hydrogels, or intravaginal elastomeric rings. Penetration enhancement may be a necessary feature of certain delivery systems, particularly when the penetrant is

Copyright © 2003 Marcel Dekker, Inc.

a biomolecular species [37], although certain absorption enhancers may induce histological damage. Where such damage is irreversible, an enhancement strategy will clearly be unacceptable.

A. Bio(muco)adhesive Semisolids

Bioadhesive polymers can control the rate of drug release from, and extend the residence time of, intravaginal delivery systems. Vaginal epithelium, although not strictly a mucosal epithelium as it does not possess secretory goblet cells, is coated with cervical mucus from vaginal fluid. Thus, the term "mucoadhesive" is preferable in this case. Mucoadhesive formulations may contain one or more therapeutic agents, or they may primarily be designed as moisturizers to control vaginal dryness.

Mucoadhesive hydrogels are weakly cross-linked polymers that are able to swell in contact with water and to spread onto the surface of mucus [38]. Their ability to achieve an intimate contact with an absorbing membrane, to localize drug delivery systems at a certain place, and to extend residence time are the main factors in their use in intravaginal drug delivery [39].

Mucoadhesion can be understood as a two-step process, in which the first adsorptive contact is governed by surface energy effects and a spreading process. In the latter phase, the diffusion of polymer chains across the polymer-mucus interface may enhance the final bond [40]. Water plays an important role in mucoadhesion. The invading water molecules liberate polymer chains from their twisted and entangled state and, thus, expose reactive sites that can bond to tissue macromolecules. The adhesion of dried hydrogels to moist tissue can be quite substantial, with water uptake from the tissue surface facilitating surface dehydration and exposing surface depressions that may act as anchoring locations [41]. Thus, the majority of hydrogels applied for intravaginal use are based on mucoadhesive polymers, including poly(acrylic acid)s and polycationic materials such as chitosan. However, other hydrogel systems are also being investigated. For example, Zulfiqar et al. [42] have prepared and characterized a range of polyurethane hydrogel networks for potential vaginal application based on poly(ethylene glycol) and hexamethylene diisocyanate using 1,1,1-tris(hydroxymethyl)ethane as the cross-linking agent. Intravaginal implantation of the hydrogel into rats produced no pathological changes in the tissue.

Spreading and retention, and consequent "messiness," of semisolid vaginal mucoadhesive systems, such as gels, are major issues in intravaginal drug delivery. Brown et al. reported a scintigraphic evaluation of vaginal dosage forms in postmenopausal women [43]. The vaginal spreading and clearance of a radiolabeled pessary formulation and a commercial polycarbophil gel was assessed in six healthy, postmenopausal female volunteers over a 6-h period by gamma scintigraphy. In five of the six subjects studied, clearance of the two formulations

Copyright © 2003 Marcel Dekker, Inc.

exhibited very little intrasubject variation. However, there was considerable intersubject variability in clearance. Importantly, there was no evidence to suggest that either of the formulations dispersed material beyond the cervix, into the uterus, in any of the subjects studied. The authors concluded that the lack of significant retention of these products in most of the volunteers had obvious implications for the delivery of therapeutic agents.

B. Vaginal Pessaries or Suppositories

Vaginal pessaries or suppositories (the terms are often used interchangeably) containing such substances as natural gums, fatty acids, alum, and rock salts were originally used in ancient Egyptian times as contraceptives. One of the earliest technical papers describing a suppository-based vaginal device was published in 1947 by Rock et al. [44]. The paper described the administration and adsorption of penicillin from a cocoa butter base in nonpregnant women with vaginitis, near-term pregnant women, and women recently postpartum. Appreciable serum levels were measured in both the vaginitis and postpartum groups, but not in the near-term group, the latter presumably due to changes in the vaginal epithelial tissue. The results also clearly demonstrated variations in absorption resulting from the menstrual cycle. These suppository/pessary systems are now most commonly used to administer drugs to promote cervical ripening prior to childbirth, and for local drug delivery to the vagina.

C. Solid Polymeric Carriers

Solid polymeric carriers represent perhaps the only class of specifically designed intravaginal drug delivery systems and comprise either solid hydrogels or elastomeric intravaginal rings. The former category relies on shape to remain in place within the vaginal space, whereas the intravaginal ring relies on its elastomeric properties, thus exerting a slight tension on the vaginal walls. Such systems are nonmessy and can be used to generate a variety of controlled-delivery profiles over periods ranging from several days to several months. Whereas the elastomeric system requires predominantly hydrophobic drugs, hydrogel systems are more suitable for hydrophilic agents.

D. Carriers for Intravaginal Delivery of Peptide and Protein Drugs

Peptide and protein drugs suffer from low bioavailability when administered orally, and thus commonly require parenteral administration. However, intravaginal delivery may offer an exciting and viable alternative for certain drugs in this category associated with female health issues [15]. Richardson et al. [37]

Copyright © 2003 Marcel Dekker, Inc.

demonstrated that vaginal absorption of insulin in sheep from either insulin solutions or a bioadhesive microsphere delivery system is significantly enhanced by the addition of lysophosphatidylcholine (LCP). While the vaginal absorption of insulin from solution was minimal, the addition of LCP resulted in a rapid rise in plasma insulin and a pronounced fall in plasma glucose levels. The absolute bioavailability of the peptide from the latter solution was 13%. The hypoglycaemic response to vaginally administered insulin was also improved using the microsphere delivery system, compared to insulin solution alone, and was further enhanced by LCP. Vaginal absorption of insulin from each formulation appeared to be influenced by the estrous cycle and was thought to correlate with changes in vaginal histology.

The ability to deliver macromolecular species intravaginally suggests the possibility of using vaginal epithelium as a portal for vaccine administration. Such work remains in the early stages, but some promising results have been reported in animal studies. Starch microspheres containing lysophosphatidylcholine have been assessed in sheep for vaginal delivery of a 40-kDa glycoprotein fragment from influenza virus hemagglutinin (TOPS) [45]. Three groups of sheep received intravaginal immunization with either a TOPS solution, TOPS/LPC as a powder formulation, or TOPS and LPC in solution, while a fourth group received intramuscular immunisation with TOPS adsorbed to an aluminium hydroxide gel. At day 45, the serum IgG and the vaginal wash IgA antibody responses induced by TOPS-DSM/LPC powder formulation were significantly greater than those induced by intravaginal immunization with the TOPS solution. However, the highest levels of antibodies in serum and vaginal wash samples were induced by intramuscular immunization with TOPS/aluminium oxide gel formulation. Intravaginal immunization with TOPS and LPC did not result in the induction of enhanced levels of antibodies in serum or vaginal wash.

Calcitonin is a polypeptide hormone used to treat postmenopausal osteoporosis, Paget's disease of the bone, and in the management of malignant hypercalcaemia. The preparation, characterization, and clinical evaluation in rats of calcitonin-containing vaginal delivery systems based on hyaluronic acid ester (HYAFF) microspheres have been reported [46,47]. HYAFF biopolymers are derived from chemically modified hyaluronic acid and are considered to be mucoadhesive [48]. HYAFF microspheres are typically prepared by a solvent evaporation method [47]. Spherical microspheres containing salmon calcitonin (sCT) and having a diameter of about 10 μm were prepared by a solvent extraction method. The efficiency of incorporation was high, with approximately 80–90% of the peptide recovered by extraction from the microspheres, while assessment of the biological activity of the peptide confirmed that the pharmacological activity of sCT was unaffected by the microsphere preparation process. The microspheres produced enhanced hypocalcaemic responses in rats compared with a simple sCT solution (22% versus 12%, respectively), but maximal effect also

Copyright © 2003 Marcel Dekker, Inc.

occurred more rapidly after administration (130 versus 195 min, respectively). Microscopic examination of the rat vaginal epithelium clearly showed the presence of numerous microspheres in the vaginal lumen and closely attached to the epithelial tissue. In a related experiment, where technetium-labeled microspheres were administered to the vagina of a sheep that had been treated with a radiolabeled gel, the distribution, spreading, and clearance of the microspheres were determined using gamma-scintigraphy. The results demonstrated the bioadhesive properties of the HYAFF microspheres under in vivo conditions and suggest that the microspheres were solely confined to the vaginal tract.

VI. FUTURE PROSPECTS FOR INTRAVAGINAL DRUG DELIVERY

Intravaginal drug delivery is increasingly of interest to the drug delivery community. Delivery systems for this route can broadly be subdivided into those that are adaptations of technologies used for other routes, such as semisolids or vaginal "tablets" that may incorporate mucoadhesive polymers or particulate carriers, and those systems specifically designed for vaginal application. In the latter category, some technologies have long been known, for example, the use of pessaries. Perhaps of greater interest are more recent developments utilizing solid polymeric carriers that can offer sustained and/or controlled delivery of a range of actives for both local and systemic administration. Thus, future developments are likely to center on specifically developed high-performance intravaginal products for female health, in combination with novel strategies for the intravaginal delivery of macromolecular actives. Thus, intravaginal delivery of biomolecules such as therapeutic peptides and proteins will be of significant interest. The nonviral delivery of DNA across vaginal epithelium may also attract attention, given the relatively low absorption barrier of this tissue. The ability to deliver biomolecules by a nonparenteral route remains the great challenge in drug delivery. The delivery of biomolecular actives that have implications for female health is therefore likely to provide one of the main drives for the further development of novel intravaginal drug delivery technologies.

REFERENCES

1. DI Macht. The absorption of drugs and poisons through the vagina. J Pharmacol Pathol 10:509–522, 1918.
2. RW Kistner. Physiology of the vagina. In: ESE Hafez, TN Evans, eds. Human Reproductive Medicine: The Human Vagina. Vol. 2. New York: North-Holland, 1978, pp. 109–120.

Copyright © 2003 Marcel Dekker, Inc.

3. J Paavonen. Physiology and ecology of the vagina. Scand J Infect Dis 40(suppl): 31–35, 1983.
4. AA Deshpande, CT Rhodes, M Danish. Intravaginal drug delivery. Drug Dev Ind Pharm 18:1225–1279, 1992.
5. VR Tindall. Jeffcoate's Principles of Gynaecology. London: Butterworth, 1987.
6. LP Gartner, JL Hiatt. Color Atlas of Histology. Baltimore: Williams & Wilkins, 1994.
7. MH Burgos, CE De Vargas-Linares. Ultrastructure of the vaginal mucosa. In: ESE Hafez, TN Evans, eds. Human Reproductive Medicine: The Human Vagina. Vol. 2. New York: North-Holland, 1978, pp. 63–93.
8. K Yu, YW Chien. Vaginal delivery and absorption of drugs. In: J Swarbrick, JC Boylan, eds. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker, 1995, pp. 153–185.
9. TS Leeson, CR Leeson, AA Pap. Textbook of Histology. Philadelphia: Saunders, 1988.
10. IR Telford. CF Bridgman. Introduction to Functional Histology. Grand Rapids, MI: Harper Collins, 1995.
11. SI Fox. Human Physiology. 6th ed. Boston: McGraw-Hill, 1999.
12. G Wagner, RJ Levin. Vaginal fluid. In: ESE Hafez, TN Evans, eds. Human Reproductive Medicine: The Human Vagina. Vol. 2. New York: North-Holland, 1978, pp. 121–137.
13. N Washington, CG Wilson. Physiological factors affecting drug delivery and availability. In: J Swarbrick, JC Boylan, eds. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker, 1995, pp. 137–169.
14. WH Masters, VE Johnson. Human Sexual Response. Boston: Little, Brown, 1966.
15. JL Richardson, L Illum. Routes of delivery—case studies: the vaginal route of peptide and protein drug delivery. Adv Drug Del Rev 8:341–366, 1992.
16. CP Wendell Smith, PM Wilson. The vulva, vagina and urethra and the musculature of the pelvic floor. In: E Philipp, M Setchell, J Ginsburg, eds. Scientific Foundations of Obstetrics and Gynaecology. London: Butterworth Heinemann, 1991, pp. 84–85.
17. DL Draper, DV Landers, MA Krohn, SL Hillier, HC Wiesenfeld, RP Heine. Levels of vaginal secretory leukocyte protease inhibitor are decreased in women with lower reproductive tract infections. Am J Obstet Gynecol 183:1243–1248, 2000.
18. AM Weber, MD Walters, LR Schover, AV Mitchinson. Vaginal anatomy and sexual function. Obstet Gynecol 86:946–949, 1995.
19. S Jaszczak, ESE Hafez. Human Reproduction, Conception and Contraception. 2nd ed. Philadelphia: Harper & Row, 1980.
20. GGG Donders, E Bosmans, A Dekeersmaecker, A Vereecken, B Van Bulck, B Spitz. Pathogenesis of abnormal vaginal bacterial flora. Am J Obstet Gynecol 182:872–878, 2000.
21. EM Curtis, L Pine. Actinomyces in the vaginas of women with and without intrauterine contraceptive devices. Am J Obstet Gynecol 140:880–884, 1981.
22. JS Welch. Quantitative and qualitative effects of douche preparations on vaginal microflora. Obstet Gynecol 81:320–321, 1993.
23. MJ Goldacre, B Watt, N Loudon, MP Vessey. Vaginal microbial flora in normal young women. Br Med J 1:1450–1459, 1979.

Copyright © 2003 Marcel Dekker, Inc.

24. S Roy, J Wilkins, DR Mishell. The effect of a contraceptive vaginal ring and oral contraceptives on the vaginal flora. Contraception 24:481–491, 1981.
25. A Schwan, T Ahren, A Victor. Effects of contraceptive vaginal ring treatment on vaginal bacteriology and cytology. Contraception 28:341–347, 1983.
26. S Roy, DR Mishell. Vaginal ring clinical studies: update. In: GI Zatuchni, A Goldsmith, JD Shelton, JJ Sciarra, eds. Long-Acting Contraceptive Delivery Systems. Philadelphia: Harper & Row, 1983, pp. 581–594.
27. HA Nash, V Brache, F Alvarez-Sanchez, TM Jackanicz, TM Harmon. Estradiol delivery by vaginal rings: potential for hormone replacement therapy. Maturitas 26: 27–33, 1997.
28. SJ Singer, GL Nicolson. The fluid mosaic model of the structure of cell membranes. Science 175:720–722, 1972.
29. YW Chien. Novel Drug Delivery Systems. 2nd ed. New York: Marcel Dekker, 1992.
30. GL Flynn, NFH Ho, S Hwang, E Owada, A Molokhia, CR Behl, WI Higuchi, T Yotsuyanagi, Y Shah, J Park. Controlled release polymeric formulations. In: DR Paul, FW Harris, eds. ACS Symposium Series 33. Washington, DC: American Chemical Society, 1976, pp. 87.
31. AP Sayani, YW Chien. Systemic delivery of peptides and proteins across absorptive mucosae. Crit Rev Ther Drug Carr Syst 13:85–184, 1996.
32. A Gursoy, A Bayhan. Testing of drug release from bioadhesive vaginal tablets. Drug Dev Ind Pharm 18:203–221, 1992.
33. A Gursoy, I Sohtorik, N Uyanik, NA Peppas. Bioadhesive controlled release systems for vaginal delivery. STP Pharma Sci 5:886–892, 1989.
34. TM Jackanicz. Vaginal ring steroid-releasing systems. In: GI Zatuchni, AJ Sobrero, JJ Speidel, J Sciarra, eds. Vaginal Contraception: New Developments. Philadelphia: Harper & Row, 1979, pp. 201–212.
35. AD Woolfson, GRE Elliott, CA Gilligan, CM Passmore. Design of an intravaginal ring for the controlled delivery of 17beta-estradiol as its 3-acetate ester. J Control Rel 61:319–328, 1999.
36. VHL Lee. Enzymatic barriers to peptide and protein absorption. Crit Rev Ther Drug Carr Syst 5:69–98, 1988.
37. JL Richardson, NF Farraj, L Illum. Enhanced vaginal absorption of insulin in sheep using lysophosphatidylcholine and a bioadhesive microsphere system. Int J Pharm 88:319–325, 1992.
38. D Duchêne, F Touchard, NA Peppas. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm 14:283–318, 1988.
39. L Brannon-Peppas. Novel vaginal drug-release applications. Adv Drug Del Rev 11: 169–177, 1993.
40. CM Lehr, JA Bouwstra, HE Boddé, HE Junginger. A surface energy analysis of mucoadhesion: contact angle measurements on polycarbophil and pig intestinal mucosa in physiologically relevant fluids. Pharm Res 9:70–75, 1992.
41. MA Longer, JR Robinson. Fundamental aspects of bioadhesion. Pharm Int 7:114–117, 1986.
42. M Zulfiqar, A Quddos, S Zulfiqar. Polyurethane networks based on poly(ethylene oxide). J Appl Polymer Sci 49:2055–2060, 1993.
43. J Brown, G Hooper, CJ Kenyon, S Haines, J Burt, JM Humphries, SP. Newman, SS.

Copyright © 2003 Marcel Dekker, Inc.

Davis, RA Sparrow, IR. Wilding. Spreading and retention of vaginal formulations in post-menopausal women as assessed by gamma scintigraphy. Pharm Res 14:1073–1078, 1997.
44. J Rock, RH Barker, WB Bacon. Vaginal absorption of penicillin. Science 105:13–15, 1947.
45. DT O'Hagan, D Rafferty, S Wharton, L Illum. Intravaginal immunization in sheep using a bioadhesive microsphere antigen delivery system. Vaccine 11:660–664, 1993.
46. JL Richardson, PA Ramires, MR Miglietta, M Rochira, L Bacelle, L Callegaro, L Benedetti. Novel vaginal delivery systems for calcitonin. 1. Evaluation of HYAFF calcitonin microspheres in rats. Int J Pharm 115:9–15, 1995.
47. M Rochira, MR Miglietta, JL Richardson, L Ferrari, M Beccaro, ML Benedetti. Novel vaginal delivery systems for calcitonin. 2. Preparation and characterization of HYAFF(R) microspheres containing calcitonin. Int J Pharm 144:19–26, 1996.
48. YD Sanzgiri, EM Topp, L Benedetti, L, VJ Stella. Evaluation of mucoadhesive properties of hyluronic acid benzyl esters. Int J Pharm 107:91–97, 1994.

Copyright © 2003 Marcel Dekker, Inc.

64
The Intravaginal Ring

R. Karl Malcolm
Queen's University Belfast, Belfast, Northern Ireland

I. INTRODUCTION

The intravaginal ring (IVR) is a flexible, doughnut-shaped drug delivery system (Fig. 1) that is inserted into the vagina for up to 12 months at a time, where it slowly releases one or more drugs to provide either a local or systemic effect. Measuring between 5 and 9.5 mm in cross-sectional diameter and between 50 and 75 mm in overall diameter, the rings have, to date, been primarily developed for the systemic delivery of contraceptive steroids and the localized and systemic delivery of steroids for hormone replacement therapy. It is likely, however, they will in the future be exploited for a much wider range of applications within women's health care in general. Not surprisingly, the IVR, which was specifically designed for the intravaginal administration of drugs, overcomes many of the disadvantages associated with more traditional vaginal drug dosage forms, such as gels, tablets, and pessaries, which are often messy, interfere with intercourse, and are poorly retained within the vagina. However, the major advantage of the IVR is its ability and versatility in providing long-term, continuous release of drug(s) at constant predetermined rates, thereby increasing cost-effectiveness, patient compliance, and therapeutic efficacy. Also, compared with implantable controlled-release devices for contraception such as Norplant®, IVRs do not require a minor surgical operation for their placement, nor, as is the case with intrauterine devices, to be fitted by a physician. Rather, the ring is placed in the vagina by the woman herself and finds its own way to the cervix, where it resides unnoticed for the treatment period before being removed.

Copyright © 2003 Marcel Dekker, Inc.

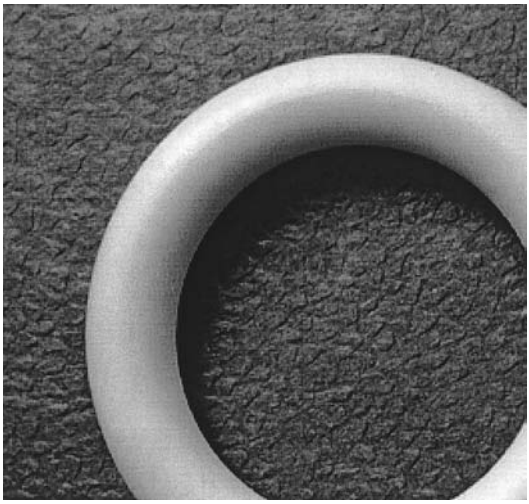


Figure 1 A silicone intravaginal ring.

II. HISTORICAL DEVELOPMENT OF THE IVR

Although the concept of incorporating drugs into polymers for controlled release has been recognized since the 1950s, it was not until 1966 that the controlled delivery of steroids from silicone rubbers was first described by Dzuik and Cook [1]. It was this finding, together with Macht's earlier work on the systemic absorption of a range of drug substances from the vagina [2], that paved the way for the 1970 patent first describing the intravaginal ring (IVR) [3]. In the same year, Mishell et al. conducted the first clinical trial of a silicone IVR homogeneously dispersed with the progestogen medroxyprogesterone acetate [4]. Although release of the steroid from the ring suppressed ovulation in all of the subjects with subsequent return after removal 28 days later, the ring also caused considerable erosion and ulceration of the vaginal tissue, damage attributed to the flat metal spring around which the rings were molded [5]. Since then, a large number of trials have been conducted investigating the clinical efficacy of the IVR for a range of therapies, mostly relating to contraceptive and hormone replacement therapies. Today, IVRs are still most commonly manufactured from medical-grade silicone (polydimethylsiloxane, PDMS) owing to certain advantageous characteristics compared with other polymer systems. These include minimal tissue reactions, biological inertness, chemical and thermal stability, and ease of fabrication. The only example of a silicone IVR currently being marketed worldwide is Estring® (Pharmacia & Upjohn, Table 1), which is used to treat local

Copyright © 2003 Marcel Dekker, Inc.

Table 1 A Description of IVRs Currently Being Marketed or Developed

IVR type	Company	Description	Ref.
ERT	Pharmacia & Upjohn Inc.	Estring—a silicone reservoir ring containing 2 mg 17β-estradiol and releasing 7.5 μg daily for use in the treatment of urogenital atrophy.	[8–16]
Contraceptive	Organon	NuvaRing—1-year combined contraceptive ring releasing 15 μg ethinylestradiol and 120 μg of the progestin etonogestrel. Phase III trials completed.	[17–24]
ERT	Galen Holdings plc	Silicone reservoir ring containing the estradiol prodrug estradiol-3-acetate for hormone replacement therapy. Phase III trials completed. Due to reach UK/European market 2000/2001.	[25,26]
HRT	Galen Holdings plc	An estradiol/progestogen reservoir IVR for continuous combined hormone replacement therapy in menopausal patients with an intact uterus. Phase II trials completed. Anticipated UK and US market—2002.	—
HRT	Galen Holdings plc	A testosterone reservoir IVR for enhancement of libido in menopausal women. Phase I trials completed.	—
Contraceptive	Population Council	A 1-year progestin-only ring containing Nestorone.	[27–32]
Contraceptive	Population Council	A 1-year combined contraceptive ring containing 15 mg of the synthetic estrogen ethinylestradiol and the progestin Nestorone. 3 weeks in, 1 week out. Phase II trials completed.	[32,33]
Contraceptive	Population Council	An IVR releasing 20 μg ethinyl estradiol plus 1 mg norethindrone acetate. Phase II trials completed.	[34–38]
Contraceptive	Population Council	A progesterone-only ring currently being manufactured and distributed in Latin America. Only suitable for breast-feeding women.	[39–42]
Contraceptive	WHO	A number of silicone rings releasing progesterone.	[43–45]
Contraceptive	WHO	A silicone vaginal ring releasing levonorgestrel at a rate of approximately 20 μg/day.	[46–49]
Urinary incontinence	FEI Technologies	Enhance UI—a silicone vaginal ring delivering oxybutynin hydrochloride for up to 1 month to the detrusor muscle of the bladder via the vaginal wall.	—
Anaesthesia	FEI Technologies	Enhance L—a silicone vaginal ring containing the local anesthetic lidocaine for anesthetization of the cervix and upper vaginal region prior to gynecological procedures.	—

Copyright © 2003 Marcel Dekker, Inc.

symptoms of urogenital atrophy. This reservoir-type ring contains 2 mg of 17β-estradiol and is designed to provide a consistent and continuous low daily dose (7.5 μg) of the estrogen for up to 3 months. Other elastomers have also been successfully employed for IVR manufacture, including styrene-butadiene-styrene block copolymers (Kraton D2109) [6] and ethylene-vinyl acetate copolymers [7]. A description of the major IVR products currently being marketed or developed is provided in Table 1.

III. IVR FORMULATIONS

A. Manufacture

Silicone IVRs are manufactured from two-component room-temperature-vulcanized (RTV-2) silicone systems. The term "two-component" refers to the fact that the polymer component is packed separately from the catalyst component, while the term "room-temperature-vulcanized" relates to the ability to cure these systems within a few hours at room temperature. In practice, however, they are cured within minutes at higher temperatures. The base polymers in these systems are linear, functionalized silicone oils of varying molecular weight to which are added reinforcing mineral fillers, such as silica. (Silicone elastomers have limited mechanical strength and need to be reinforced through the addition of inert fillers—the presence of the filler accounts for the off-white, opaque appearance of silicone IVRs). A multifunctional cross-linking agent reacts with the linear silicone polymers in the presence of a catalyst to produce the elastomer network. The functionalized silicone polymer, the reinforcing filler, and the processing fluid are generally purchased premixed and are termed the "elastomer base." These base materials are readily available from various manufacturers/suppliers. The addition of the cross-linking agent to the elastomer base produces the elastomer mix, while the subsequent addition of a drug substance produces an active elastomer mix. The processing fluid is added to modify the viscosity of the elastomer base for the purposes of injection molding.

Two curing reactions—condensation and addition cure—have been successfully employed for the purpose of manufacturing IVRs by reaction injection molding of RTV-2 silicones. The more commonly employed condensation cure involves the tin-catalyzed reaction between a difunctional hydroxy-terminated PDMS and a tetra-alkoxysilane cross-linking agent (e.g., tetrapropoxysilane), as described in Figure 2. The reaction produces an alcohol by-product which, if capable of dissolving the drug, can modify the drug release. The main advantage of this curing system is a fast cure time—2 min at 80°C is typical.

The second curing reaction for RTV-2 silicones is the platinum-catalyzed addition reaction that occurs between a vinyl-terminated silicone (Si-CH$=$CH$_2$) and a hydride-substituted silicone (-SiH) (Fig. 3). The double bond of the silicone

Copyright © 2003 Marcel Dekker, Inc.

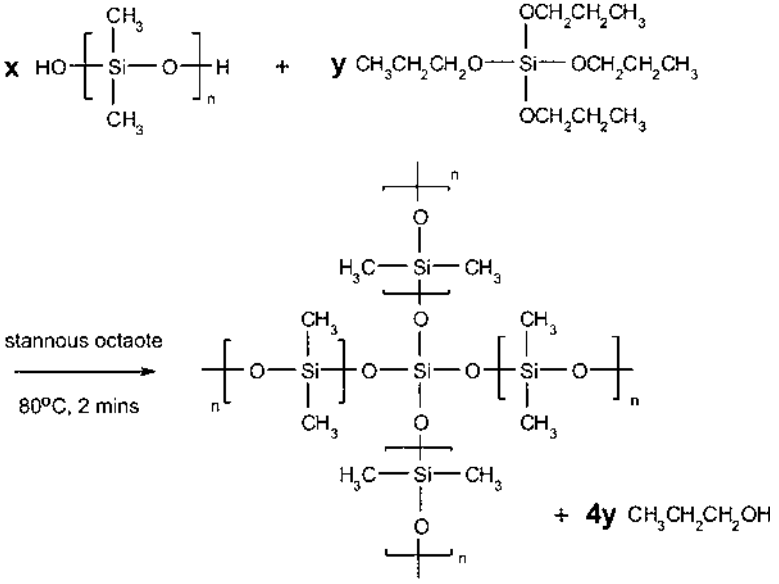


Figure 2 Silicone condensation cure mechanism.

vinyl group (Si-CH═CH_2) complexes with the platinum atom of the catalyst, H[(C_3H_6)$PtCl_3$], which facilitates addition of the hydride group (-SiH) to the vinyl group thus forming an ethylene linkage between neighboring silicone chains. The major advantages of this curing mechanism include the avoidance of volatile by-products, controllable cure rates, and no postcure requirements. However, the addition reaction is inhibited by the presence of unconjugated double bonds and certain amine functionalities; thus, for the many drugs containing these groups, IVRs cannot be made according to this method.

B. IVR Types and Release Mechanisms

1. Homogenous Dispersion IVR

The simplest IVR device, manufactured by a single injection of an active elastomer mix, contains drug homogeneously dispersed throughout the polymer matrix (Fig. 4A). During in vitro drug release from these matrix systems, the whole surface area of the ring is exposed to the dissolution medium and drug release occurs in several distinctive stages. First, drug molecules within the immobilized drug particles present at the surface of the ring dissociate from the crystal lattice and dissolve into the release medium, thus giving rise to a burst effect and creat-

Copyright © 2003 Marcel Dekker, Inc.

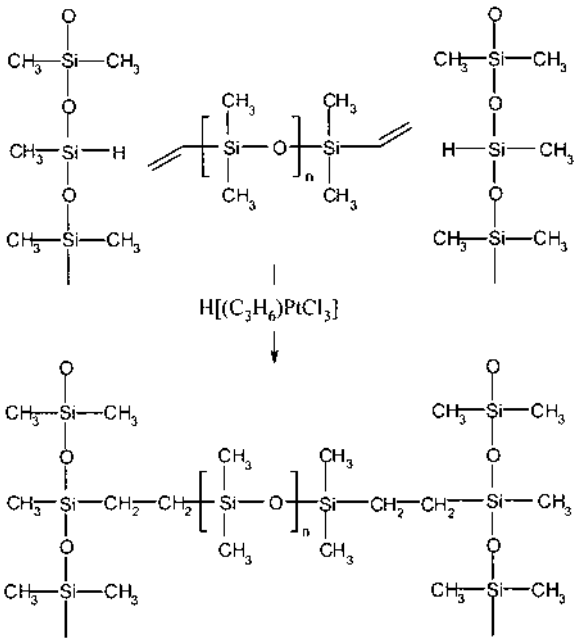


Figure 3 Silicone addition cure mechanism.

ing a concentration gradient within the IVR that thermodynamically drives the release process. Drug molecules near the ring surface then diffuse through the polymer and are subsequently released. As drug release continues, a drug depletion zone is created that separates the drug-deficient surface from the inner drug-loaded region of the polymer matrix. (It is also likely that water is able to penetrate into the channels created by drug depletion and, thus, dissolve the drug present at the depletion boundary.) The surface area of this inward-moving depletion boundary decreases, with simultaneous increase in the thickness of the drug-depleted zone. Therefore, the amount of drug released decreases with time as the drug close to the surface of the ring becomes exhausted and the diffusional pathway for the remaining drug increases. A plot of cumulative drug release versus time yields a concentration-dependent release profile (Fig. 4A). (A cumulative release versus $\sqrt{t}$ plot shows a linear relationship.) The in vitro release of drug from a matrix IVR under sink conditions is described by the Higuchi equation [Eq. (1)] [50], a polymer matrix diffusion-controlled model, where Q is the cumulative release per unit area, D_{SIL} is the drug diffusion coefficient in silicone, C_{SIL} is the drug solubility in the silicone elastomer, A is the drug loading per unit volume, and t is time. Two of these parameters are physicochemical properties

Copyright © 2003 Marcel Dekker, Inc.

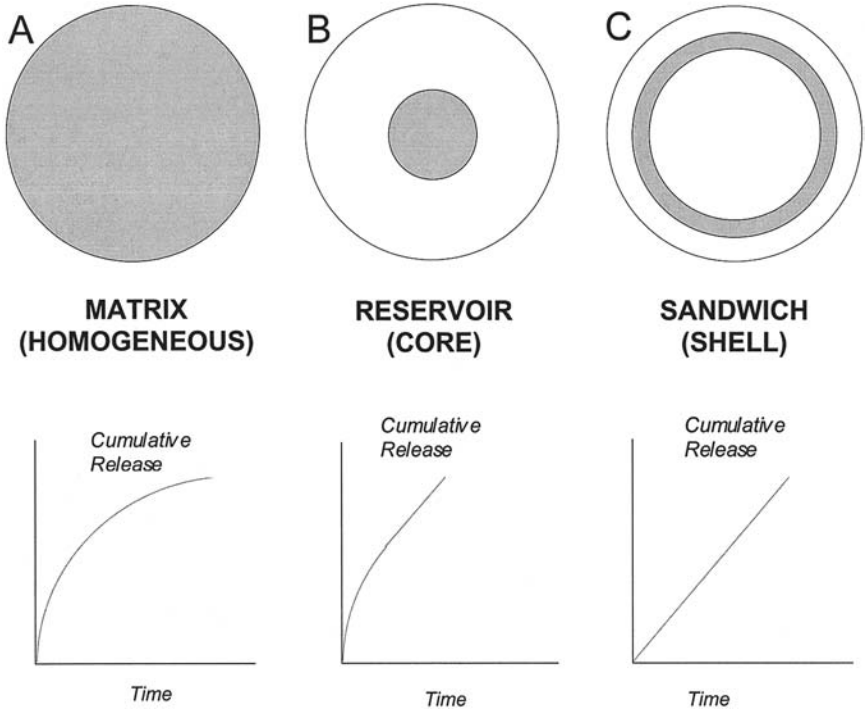


Figure 4 IVR types and release profiles.

associated with the drug and the polymer (D_{SIL} and C_{SIL}), whereas the surface area of the ring ($s = 4\pi^2 bc$, where b is the cross-sectional radius and c the external radius) and the drug loading (A) are device-dependent.

$$Q = \sqrt{D_{SIL}(2A - C_{SIL})C_{SIL}t} \quad (1)$$

2. Reservoir (Core) IVR

In the reservoir or core IVR, the drug is located within a centralized core that is surrounded by a drug-free silicone sheath (Fig. 4B). Thus, drug molecules at the core/sheath interface must first dissociate themselves from the crystal lattice and dissolve into the surrounding silicone elastomer, before diffusing through the nonmedicated sheath and finally partitioning into the elution medium surrounding the device. One of the main advantages of reservoir over matrix rings, aside from the fact that they release drug in a zero-order fashion, is that their release characteristics can be readily modified, either by changing the thickness of the

Copyright © 2003 Marcel Dekker, Inc.

sheath (h_m) layer or by varying the core length (L). Decreasing the sheath thickness provides a shorter diffusional pathway for the drug and, therefore, enhances the release rate, according to Eq. (2). The effect of core length on in vitro release is described by Crank's equation [51] [Eq. (3)] where L is the core length, a is the cross-sectional diameter of the core, and b is the cross-sectional diameter of the sheath. Smaller core lengths lead to reduced release rates. Also, multiple drug administration can be achieved by employing several small drug-loaded cores containing different drugs. Several examples of estrogen plus progestogen reservoir IVRs are described in Table 1.

$$Q = \frac{D_{SIL}C_{SIL}t}{h_m} \tag{2}$$

$$Q = \frac{2\pi D_{SIL}C_{SIL}Lt}{ln(b/a)} \tag{3}$$

Reservoir rings are manufactured in several steps. A drug-loaded core is first prepared either by reaction injection molding (low drug concentrations, typically <30%) or by extrusion (high drug concentrations, 30–70%) of an active elastomer mix. The full cores may be cut into smaller core lengths depending on the required release rate. The full or partial core(s) are then encapsulated with silicone elastomer in two stages to produce the full reservoir ring. Although a perfect zero-order-release profile is theoretically possible with these reservoir systems, a burst effect often lasting several days is often observed with the condensation-cured silicone IVRs (Fig. 4B). This has been attributed to the presence of solid drug in the sheath layer of the IVR, a consequence of the ability of the propanol condensation by-product from the curing reaction to dissolve and transport some of the drug from the core to the sheath before evaporating [26]. The daily and cumulative release plots of estradiol from a reservoir IVR, shown in Figure 5, demonstrate a two-day burst effect followed by a zero-order-release profile [26].

3. Sandwich (Shell) IVR

The sandwich, or shell, IVR design consists of a narrow drug-containing layer located a fraction of a millimeter below the outer surface of the ring and positioned between a nonmedicated central core and a nonmedicated outer band. The position of the drug core close to the surface ensures sandwich IVRs are best suited to the delivery of drugs having poor polymer diffusion characteristics. The small, constant release of drug from this IVR system not only reduces side effects compared with matrix devices, but also minimizes the cost of the device owing to the relatively low drug loading. A sandwich ring, releasing 4 mg progesterone per day, was first fabricated by Burton in 1978 employing multistep molding

Copyright © 2003 Marcel Dekker, Inc.

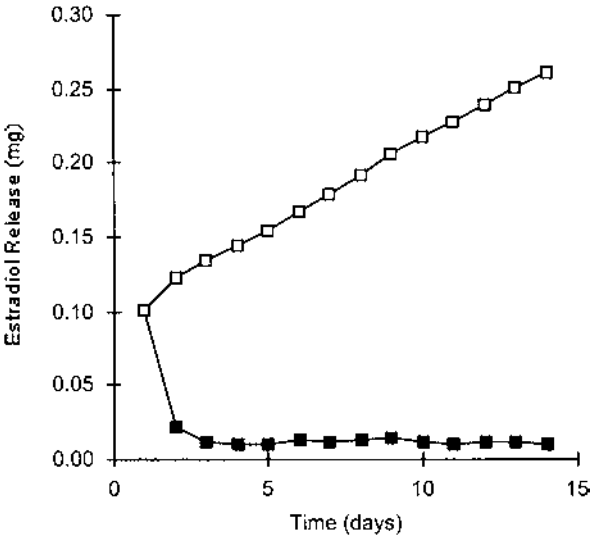


Figure 5 The cumulative and daily release of 17β-estradiol from a full-core reservoir IVR.

process and using silicone tubing as the outer layer [52]. A detailed description of the manufacturing process for these rings is given by Jackanicz [53].

IV. IVR RESEARCH AND DEVELOPMENT

Several excellent reviews have been published describing the various developments in IVR between 1970 and 1992 [54–58]. Although research on IVRs began in the 1960s and the number of rings under development has since proliferated, it was not until 1993 that the first IVR, Estring (Table 1), was approved and marketed in Sweden. Even today, Estring is the only IVR on the market, although several others are likely to be marketed early in 2001, notably Galen's estradiol prodrug ring containing 17β-estradiol-3-acetate and Organon's combined contraceptive ring (Nuvaring®). It is interesting to note that IVRs for ERT have reached market before their contraceptive counterparts, despite the fact that most time and effort has been spent developing the latter. There are a number of reasons why contraceptive IVRs have failed to match earlier expectations. Over the past 30 years, many pharmaceutical companies cut back or terminated their contraceptive research efforts, primarily due to product liability costs brought about by sizable legal judgments against some contraceptive manufacturers and corporate

Copyright © 2003 Marcel Dekker, Inc.

frustration with product safety regulation [59]. Also, the explosion of sexually transmitted diseases, in particular AIDS, has led to a change in public opinion concerning such "hi-tech" delivery systems as the IVR, since, although they offer many advantages, they do not offer the barrier protection of "low-tech" methods such as condoms. Finally, many companies believe that the profitable contraceptive markets in developed countries are already mature and have little additional profit potential [60]: in the absence of a revolutionary new method that could force its way into a crowded market, most companies prefer to continue selling their existing product line rather than invest huge sums into research on methods that might not produce any greater profits. IVRs had their own inherent problems too, with research efforts slowed by two serious problems. In 1987, Dow Corning stopped producing a chemical crucial to the fabrication of one of the materials used in many of the vaginal rings. As a result, most had to be redesigned, with concomitant delays in testing and development. Then came the discovery in 1992 of vaginal lesions in some women using IVRs [61]. Most work on vaginal rings was halted while special studies of the vaginal effects of ring use were conducted. However, results indicated that such lesions also occurred among nonusers and did not appear to be associated with the ring itself [28,62].

Several contraceptive IVRs, apart from Nuvaring, are currently undergoing clinical investigation. Two types are currently being studied: those that release only a progestogen, and those that release both a progestogen and an estrogen. The biggest advantage of the progestogen-only rings is that they can be used by women who are breast-feeding; their chief disadvantage is one shared by other progestogen-only contraceptives—irregular menstrual bleeding. At the start of the 1990s, among four progestogen-releasing rings at various stages of development, a levonorgestrel-releasing ring developed by the World Health Organization was closest to going into general use. This device had a projected life span of 3 months, had undergone extensive testing in Great Britain, and was about to enter large-scale production. However, its introduction was postponed at a very late stage when vaginal irritation was detected in a small number of users [61]. A vaginal ring with a projected life span of 1 year or more has been developed by the Population Council; this ring steadily releases a very low dose of a progestogen called Nestorone®. The technology developers anticipate that both breast-feeding women and normally ovulating women will be able to use this ring. Finally, Population Council researchers have also developed a ring that releases progesterone, a natural progestogen, and will be used exclusively by breast-feeding women.

The Population Council is also responsible for two IVRs that release a combination of progestogen and estrogen: the first releases norethindrone acetate and ethinyl estradiol and can be used for up to 1 year; the second contains Nestorone and ethinyl estradiol, and is expected to be effective for 6–12 months. Both are in early phases of human trials; the Council expects to wait until full data

Copyright © 2003 Marcel Dekker, Inc.

have been collected on both versions of the combined ring, and then proceed to market with the better design.

V. FUTURE DIRECTIONS FOR THE IVR

The versatility of the IVR drug delivery system coupled with its inherent advantages over other vaginal dosage forms will inevitably lead to its exploitation in other areas of women's health care. These are likely to include (a) delivery of vaccines, (b) delivery of peptides, (c) treatment and/or prevention of sexually transmitted diseases, and (d) treatment of vaginal infections. Several preliminary reports of such approaches are already appearing in the literature. For example, danazol, routinely administered orally to inhibit ovulation and to treat pelvic endometriosis, has been administered vaginally using a 1500-mg-loaded IVR for successful treatment of the latter [63]. It appears that the drug is absorbed through the vaginal mucosa and reaches the deeply infiltrating endometriosis via diffusion. Also, ferritin-loaded rings, manufactured from ethylene-vinyl acetate copolymer, have been used to induce high-titer, long-lasting antibody responses in the vagina of mice [64]: mucosal delivery of antigens is known to produce a better local response than systemic delivery. It might also be possible to develop an IVR releasing a spermicidal agent, such as nonoxynol-9, hence overcoming the inconvenience of current formulations [65].

To adapt IVRs to release a wider range of drug substances, it will be necessary to either modify existing silicone systems or employ new polymer materials. Silicones have been useful in that their excellent diffusional properties, a reflection of their very low glass transition temperature, have allowed drugs to be delivered in therapeutic amounts that might have been impossible with other polymer systems. Yet, their inherently hydrophobic nature has also limited permeants to similarly hydrophobic substances, such as steroids. Many studies have reported the inclusion of hydrophilic excipients into silicone elastomer as a means of modifying drug release [66–68], and this approach may well prove useful in the development of IVRs for delivery of less-hydrophobic drugs, such as the many antimicrobial drugs used to treat vaginal infections.

REFERENCES

1. PJ Dzuik, B Cook. Passage of steroids through silicone rubber. Endocrinology 87: 208–211, 1966.
2. DI Macht. The absorption of drugs and poisons through the vagina. J Pharmacol Pathol 10:509–522, 1918.
3. GW Duncan. US patent 3,545,439, 1970.

Copyright © 2003 Marcel Dekker, Inc.

4. DR Mishell, M Talas, AF Parlow, DL Moyer. Contraception by means of a silastic vaginal ring impregnated with medroxyprogesterone acetate. Am J Obstet Gynecol 107:100–107, 1970.
5. DR Mishell, ME Lumkin. Contraceptive effect of varying doses of progestogen in Silastic vaginal rings. Fertil Steril 21:99–103, 1970.
6. J Vartiainen, T Wahlstrom, CG Nilsson. Effects and acceptability of a new 17β-estradiol-releasing vaginal ring in the treatment of postmenopausal complaints. Maturitas 117:129–137, 1993.
7. F Roumen, T Dieben. Clinical acceptability of an ethylene-vinyl acetate nonmedicated vaginal ring. Contraception 59:59–62, 1999.
8. G Lose, E. Englev. Oestradiol-releasing vaginal ring versus oestriol vaginal pessaries in the treatment of bothersome lower urinary tract symptoms. Br J Obstet Gynecol 107:1029–1034, 2000.
9. BC Eriksen. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol 180:1072–1079, 1999.
10. R Barentsen, PHM vandeWeijer, JHN Schram. Continuous low dose estradiol released from a vaginal ring versus estriol vaginal cream for urogenital atrophy. Eur J Obstet Gynecol Reprod Biol 71:73–80, 1997.
11. D Botsis, D Kassanos, D Kalogirou, G Antoniou, P Karakitsos, PA Zourlas. A comparative study of an estradiol-releasing vaginal ring versus tibolone in postmenopausal women: a transvaginal color Doppler study. Maturitas 27:77–83, 1997.
12. D Kalogirou, G Antoniou, P Karakitsos, O Kalogirou, D Antoniou, L Giannikos. A comparative study of the effects of an estradiol-releasing vaginal ring combined with an oral gestagen versus transdermal estrogen combined with a levonorgestrel-releasing IUD: Clinical findings and endometrial response. Int J Fertil 41:522–527, 1996.
13. L Henriksson, M Stjernquist, L Boquist, I Cedergren, I Selinus. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. Am J Obstet Gynecol 174:85–92, 1996.
14. J Gabrielsson, I Wallenbeck, G Larsson, L Birgerson, G Heimer. New kinetic data on estradiol in light of the vaginal ring concept. Maturitas 22:S35–S39, 1995.
15. G Schmidt, SB Andersson, O Nordle, CJ Johansson, PO Gunnarsson. Release of 17-beta-estradiol from a vaginal ring in postmenopausal women—pharmacokinetic evaluation. Gyneco Obste Invest 38:253–260, 1994.
16. P Smith, G Heimer, M Lindskog, U Ulmsten. Oestradiol-releasing vaginal ring for treatment of postmenopausal urogenital atrophy. Maturitas 16:145–154, 1993.
17. CJ Timmer, TMT Mulders. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. Clin Pharmacokinet 39:233–242, 2000.
18. FJME Roumen, ME Boon, D van Velzen, TOM Dieben, HJT Coelingh Bennink. The cervico-vaginal epithelium during 20 cycles' use of a combined contraceptive vaginal ring. Hum Reprod 11:2443–2448, 1996.
19. GC Davies, TOM Dieben, LX Feng, JR Newton. Ovarian activity and bleeding pat-

Copyright © 2003 Marcel Dekker, Inc.

terns during extended continuous use of a combined contraceptive vaginal ring, Contraception 46:269–278, 1992.
20. GC Davies, TOM Dieben, LX Feng, JR Newton. The effects of a combined contraceptive vaginal ring releasing ethinyloestradiol and 3-ketodesogestrel on vaginal flora. Contraception 45:511–518, 1992.
21. D Apter, B Cacciatore, UH Stenman. Clinical performance and endocrine profiles of contraceptive vaginal rings releasing 3-ketodesogestrel and ethinyloestradiol. Contraception 42:285–295, 1990.
22. SE Olsson, V Odlind. Contraception with a vaginal ring releasing ethinyloestradiol and 3-ketodesogestrel. Contraception 42:563–572, 1990.
23. F Roumen, T Dieben, R Assendorp, P Bouckaert. The clinical acceptability of a non-medicated vaginal ring. Contraception 42:201–207, 1990.
24. CJ Timmer, D Apter, G Voortman. Pharmacokinetics of 3-ketodesogestrel and ethinyloestradiol released from different types of contraceptive vaginal rings. Contraception 42:62, 1993.
25. AD Woolfson, GRE Elliott, CA Gilligan, CM Passmore. Design of an intravaginal ring for the controlled delivery of 17β-estradiol as its 3-acetate ester. J Control Rel 61:319–328, 1999.
26. JA Russell, RK Malcolm, K Campbell, AD Woolfson. High performance liquid chromatographic determination of 17β-estradiol and 17β-estradiol-3-acetate solubilities and diffusion coefficients in silicone elastomeric intravaginal rings. J Chrom Biom B 744:157–163, 2000.
27. IS Fraser, E Weisberg, E Minehan, EDB Johansson. A detailed analysis of menstrual blood loss in women using Norplant and Nesterone progestogen-only contraceptive implants or vaginal rings. Contraception 61:241–251, 2000.
28. IS Fraser, M Lacarra, DR Mishell. Vaginal epithelial surface appearances in women using vaginal rings for contraception. Contraception 61:131–138, 2000.
29. Z Tuba, CW Bardin, A Dancsi. Synthesis and biological activity of a new progestogen, 14-methylene-17-alpha-hydroxy-18-methyl-19-norpregn-4-ene-3,20-dione acetate. Steroids 65:266–274, 2000.
30. A Robbins, CW Bardin. Nestorone, progestin—the ideal progestin for use in controlled release delivery systems. Ann NY Acad Sci 828:38–46, 1997.
31. F Li, N Kumar, YY Tsong. Synthesis and progestational activity of 16-methylene-17 alpha-hydroxy-19-norpregn-4-ene-3,20-dione and its derivatives. Steroids 62:403–408, 1997.
32. F Alvarez-Sanchez, V Brache, T Jackanicz, A Faundes. Evaluation of four different contraceptive vaginal rings: steroid serum levels, luteal activity, bleeding control and lipid profiles. Contraception 46:387–398, 1992.
33. TM Jackanicz, F Alvarez-Sanchez, V Brache, K Elomaa, B Charbonnel, P Bouchard. Clinical studies of Nestorone progestin/ethynylestradiol contraceptive rings. Proceedings of the 4th Congress of the European Society of Contraception. Eur J Cont Reprod Health Care 1:136, 1996.
34. E Weisberg, IS Fraser, DR Mishell Jr., M Lacarra, P Darney, T Jackanicz. A comparative study of two contraceptive vaginal rings releasing norethindrone acetate and differing doses of ethinyl estradiol. Contraception 59:305–310, 1999.
35. E Weisberg, IS Fraser, M Lacarra, DR Mishell Jr, F Alvarez, V Brache, HA Nash.

Copyright © 2003 Marcel Dekker, Inc.

Efficacy, bleeding patterns, and side effects of a 1-year contraceptive vaginal ring. Contraception 59:311–318, 1999.
36. E Weisberg, IS Fraser, M Lacarra, DR Mishell Jr, T Jackanicz. Effect of different insertion regimens on side effects with a combination contraceptive vaginal ring. Contraception 56:233–239, 1997.
37. E Weisberg, IS Fraser, DR Mishell Jr., M Lacarra, CW Bardin. The acceptability of a combined oestrogen/progestogen contraceptive vaginal ring. Contraception 51: 39–44, 1995.
38. SA Ballagh, DR Mishell, Jr., M Lacarra, D Shoupe, T Jackanicz, P Eggena. A contraceptive vaginal ring releasing norethindrone acetate and ethinyl estradiol, Contraception 50:517–533, 1994.
39. R Massai, P Miranda, P Valdes, P Lavin, A Zepeda, ME Casado, MA Silva, G Fetis, C Bravo, O Chandia, O Peralta, HB Croxatto, S Diaz. Pre-registration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. Contraception 60:9–14, 1999.
40. JH Chen, SC Wu, WQ Shao, MH Zou, J Hu, L Cong, C Miao, C Wang, J Dong, J Gao, BL Xaio. The comparative trial of TCu 380A IUD and progesterone-releasing vaginal ring used by lactating women. Contraception 57:371–379, 1998.
41. S Diaz, A Zepeda, X Maturana, MV Reyes, P Miranda, ME Casado, O Peralta, HB Croxatto. Fertility Regulation in Nursing Women. IX. Contraceptive performance, duration of lactation, infant growth, and bleeding patterns during use of progesterone vaginal rings, progestin-only pills, Norplant implants, and Copper T 380-A intrauterine devices. Contraception 56:223–232, 1997.
42. I Sivin, S Diaz, HB Croxatto, P Miranda, M Shaaban, EH Sayed, B Xiao, S Wu, M Du, F Alvarez, V Brache, S Basnayake, T McCarthy, M Lacarra, DR Mishell Jr., S Koetsawang, J Stern, T Jackanicz. Contraceptives for lactating women: a comparative trial of a progesterone-releasing vaginal ring and the Copper T 380A IUD. Contraception 55:225–232, 1997.
43. BM Landgren, B Jonsson, SZ Cekan. The effect of small doses of progesterone released from two types of vaginal rings on ovarian activity and bleeding patterns during the first postpartum year. Contraception 51:255–260, 1995.
44. BM Landgren, PE Hall, SZ Cekan. Progesterone-releasing vaginal rings for use in postpartum contraception. II. Pharmokinetic profiles in women. Contraception 45: 343–349, 1992.
45. SA Matlin, A Belenguer, PE Hall. Progesterone-releasing vaginal rings for use in postpartum contraception. I. In vitro release rates of progesterone from core-loaded rings. Contraception 45:329–341, 1992.
46. BM Landgren, AR Aedo, E Johannisson, SZ Cekan. Pharmacokinetic and pharmacodynamic effects of vaginal rings releasing levonorgestrel at a rate of 27 μg/24 hours: a pilot study. Contraception 49:139–150, 1994.
47. BM Landgren, AR Aedo, E Johannisson, SZ Cekan. Studies on a vaginal ring releasing levonorgestrel at an initial rate of 27 μg/24h when used alone or in combination with transdermal systems releasing estradiol. Contraception 50:87–100, 1994.
48. World Health Organisation task force on long-acting agents for fertility regulation. Special Programme of Research, Development and Research Training in Human

Copyright © 2003 Marcel Dekker, Inc.

Reproduction. Menstrual blood loss with use of a vaginal ring releasing 20 μg levonorgestrel per day. Contraception 47:455–468, 1993.
49. World Health Organisation task force on long-acting agents for fertility regulation. Microdose intravaginal levonorgestrel contraception: a multicentre clinical trial. 1. Contraceptive efficacy and side effects. Contraception 41:105–124, 1990.
50. T Higuchi. Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 52:1145, 1963.
51. J Crank. The Mathematics of Diffusion. London: Oxford at the Clarendon Press, 1956.
52. FG Burton. Fabrication and testing of vaginal contraceptive devices designed for release of prespecified dose levels of steroids. Contraception 17:221–230, 1978.
53. TM Jackanicz. Levonorgestrel and estradiol release from an improved contraceptive vaginal ring. Contraception 24:323–339, 1981.
54. DR Mishell Jr. Vaginal contraceptive rings. Ann Med 25:191–197, 1993.
55. L Brannon-Peppas. Novel vaginal drug-release applications. Adv Drug Del Rev 11: 169–177, 1993.
56. E Diczfalusy. New developments in oral, injectable and implantable contraceptives, vaginal rings and intrauterine devices—a review. Contraception 33:7–23, 1986.
57. PJ Rowe. Steroid-releasing vaginal rings: a review. Fertility and Sterility: The Proceedings of the 11th Congress on Fertility and Sterility (Dublin), Lancaster. 27:301–309, 1983.
58. AD Woolfson, RK Malcolm, R Gallagher. Drug delivery by the intravaginal route. Crit Rev Ther Drug Carr Syst 17:509–555, 2000.
59. M Klitisch. Still waiting for the contraceptive revolution. Family Planning Perspect 27:6, 1995. (See also: http://www.amaassn.org/special/contra/library/readroom/other96/gutt.htm).
60. Program for Appropriate Technology in Health. Enhancing the private sector's role in contraceptive research and development. In: PFA Van Look, G Perez-Palacios, eds. Contraceptive Research and Development, 1984–1994: The Road to Mexico City and Beyond. Oxford, UK: Oxford University Press, 1994.
61. W Bounds, A Szarewski, D Lowe, J Guillebaud. Preliminary report of unexpected local reactions to a progestogen-releasing contraceptive vaginal ring. Eur J Obstet Gynecol Reprod Biol 48:123–125, 1993.
62. IS Fraser, P Lahteenmaki, K Elomaa, M Lacarra, DR Mishell, F Alvarez, V Brache, E Weisberg, M Hickey, P Vallentine, HA Nash. Variations in vaginal epithelial surface appearance determined by colposcopic inspection in healthy, sexually active women. Hum Reprod 14:1974–1978, 1999.
63. M Igarashi, M Iizuka, Y Ibuki. Novel vaginal danazol ring therapy for pelvic endometriosism in particular deeply infiltrating endometriosis. Hum Reprod 13:1952–1956, 1998.
64. TL Wyatt, KJ Waley, RA Cone, WM Saltzman. Antigen-releasing polymer rings and microspheres stimulate mucosal immunity in the vagina. J Control Rel 50:93–102, 1998.
65. WM Saltzman, LB Tena. Spermicide permeation through biocompatible polymers. Contraception 43:497–505, 1991.

Copyright © 2003 Marcel Dekker, Inc.

66. R Tarantino, D Adair, S Bolton. In vitro and in vivo release of salicylic acid from povidone/polydimethylsiloxane matrices. Drug Dev Ind Pharm 16:1217–1231, 1990.
67. V Carelli, G Di Colo, E Nannipieri, MF Serafini. Evaluation of a silicone based matrix containing crosslinked polyethylene glycol as a controlled drug delivery system for potential oral application. J Control Rel 33:153–162, 1995.
68. G Di Colo, V Carelli, E Nannipieri, MF Serafini, D Vitale. Effect of water-soluble additives on drug release from silicone rubber matrices. II. Sustained release of prednisolone from non-swelling devices. Int J Pharm 30:1–7, 1986.

Copyright © 2003 Marcel Dekker, Inc.

65
SupraVail Vaginal Gel

Mathew Leigh
Phares Drug Delivery AG, Muttenz, Switzerland

I. INTRODUCTION

An optimized vaginal delivery system should provide the opportunity for controlled and prolonged release of drugs. It should also be designed to maximize the efficacy of the active drug and minimize the cost. While a number of vaginal drug delivery systems have been developed (e.g., containing permeability/stability-enhancing and bioadhesive agents), phospholipids offer many benefits as a platform for vaginal drug delivery.

II. PHOSPHOLIPIDS

A. Definition

The term "phospholipid" refers to a lipid-containing phosphoric acid as a mono- or diester. Phospholipids comprise a phosphoric head attached to a glycerol backbone, which in turn is linked to the hydrophobic fatty acids. Two types of phospholipids exist—glycerophospholipids (phosphodiglycerides) and sphingophospholipids. The glycerophospholipids are the most abundant and possess a hydrophilic head group containing phosphorus and one other chemical subgroup (e.g., choline, ethanolamine, inositol, or serine).

B. Occurrence and Uses

Phospholipids are a functionally versatile class of compounds that are ubiquitously distributed in human, animal, plant, and microorganism cells. They are important elements in the structure of biological membranes acting essentially

Copyright © 2003 Marcel Dekker, Inc.

as the "solvent matrix." They have found widespread application within cosmetic, agriculture-food, and pharmaceutical domains. Phospholipids are traditionally used as emulsifiers in many pharmaceutical products and are the key components of liposome formulations.

C. Toxicology

Phospholipids are extremely well tolerated from a physiological standpoint, and their highly favorable toxicity profile has prompted widespread inclusion in many formulations. They are natural substances that occur in foods and are accepted by many regulatory authorities as toxicologically safe. Lecithin (primarily a mixture of phospholipids) is GRAS listed ("generally recognized as safe") by the Food and Drug Administration (FDA) and appears in many drug monographs. Lecithin is also listed in the FDA Inactive Ingredients Guide (inhalations, IM and IV injections, oral capsules, suspensions and tablets, rectal, topical, and vaginal preparations). Phospholipids are included in nonparenteral and parenteral medicines licensed in England and are universally accepted as food additives and cosmetic excipients within the European Community. Furthermore, no apparent adverse side effects arise from phospholipid fractions that have been purified through column chromatography.

III. LIPOSOMES

Phospholipids are the key components of liposomes. Liposomes are vesicular structures that are widely utilized in topical delivery systems and are versatile platforms for drug delivery. They have been used in vaginal therapy with promising results [1–5], although research in this area is fairly limited. Liposomes have the potential to associate amphipathic or lipophilic drugs and can be modified to impart controlled-release properties. However, preformed liposomes are not ideal delivery platforms and have a number of attendant problems. Their major drawbacks are limited drug loading and poor storage stability; it is difficult to attain effective drug loading within the liposomes and drug molecules often leak from the structures. Furthermore, energy-intensive manufacturing techniques such as extrusion, high-pressure homogenization, and solvent evaporation methods are time-consuming and expensive. Not surprisingly, this tends to promote the development of high-cost niche products.

IV. PROLIPOSOMES

The proliposome approach was developed as a straightforward, reproducible, and reliable manufacturing technique for large-scale production of liposome disper-

Copyright © 2003 Marcel Dekker, Inc.

sions [6,7]. Today, it is one of the most cost-effective and widely used methods for producing commercial liposome products. The technology is based upon the intrinsic property of hydrated membrane lipids to form vesicles on contact with water. A typical formulation consists of suitable fractions of phospholipids with an active component, which may be lipophilic or amphipathic. The formulation does not, however, contain sufficient water to allow liposome formation under storage conditions. Liposomes are formed only when the formulation comes into contact with a moist aqueous environment such as found on the skin or mucosal surfaces. It is designed particularly for the molecular dispersion and delivery of water-insoluble materials where association efficiencies approaching 100% can be achieved. Proliposomes have been employed as a basis for a number of site-specific drug delivery approaches.

V. SUPRAVAIL MUCOCUTANEOUS DELIVERY

A. Background

SupraVail™ is the name given to the platform technology for delivering poorly water soluble drugs as molecular associates to maximize bioavailability. These associates are formed from lipid complexes, which may be liquids, semisolids, or solids. The complexes can be incorporated into various dosage forms for different routes of administration. SupraVail dosage forms have the intrinsic capacity to form lipid aggregates where the drug is in molecular association. Depending upon the type of phospholipids selected, these structures may be vesicles, micelles, or mixed micelles. The SupraVail technology designed for topical and mucosal applications, including intravaginal drug delivery, is a semisolid proliposome gel.

The formulations utilize fractionated phospholipids to form vesicular structures in vivo, triggered by the aqueous environment found on mucosal surfaces. These have a high potential to associate with both lipophilic and hydrophilic compounds. The type of phospholipid fraction used for mucocutaneous application will depend on the physicochemical properties of the drug and also on the required characteristics for the formulation. The key to SupraVail delivery is, first, to disperse the drug in a monomolecular state within phospholipid bilayers. Second, in the presence of excess water the bilayers readily convert into discrete vesicular structures. The important feature in this process is that the drug should remain associated with the vesicles even after conversion. While the phospholipid and drug form the basis of the formulation, a number of excipients can be readily incorporated to optimize the product characteristics.

B. SupraVail Vaginal Gels

A gel presentation is particularly suitable for vaginal administration. It is non-greasy, aesthetically appealing, and offers the potential for improved drug reten-

Copyright © 2003 Marcel Dekker, Inc.

tion. In SupraVail gels, the phospholipid adopts a liquid crystalline matrix and forms a bilayered translucent gel. Lipophilic drugs readily associate with the phospholipid molecules. The SupraVail gel is particularly suitable for incorporation of lipophilic drugs and thus acts an excellent carrier for antifungal and steroid compounds. On contact with the mucosal surface, the bilayered gel formulation converts readily in vivo to vesicular structures.

A typical SupraVail formulation consists of three essential components; phospholipids, hydrophilic media, and active compound. Other excipients, such as polymers to improve bioadhesion and stabilizers (e.g., buffers and antioxidants), may also be added if necessary. Figure 1 shows a freeze fracture of a bilayered gel and Figure 2 shows a freeze fracture of a liposome dispersion formed from a proliposome gel after contact with water.

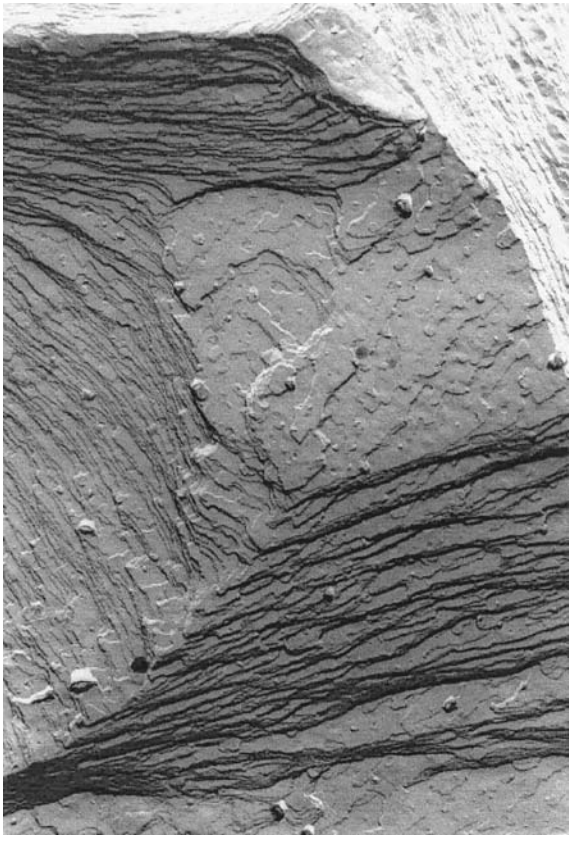


Figure 1 Freeze fracture of a bilayered gel.

Copyright © 2003 Marcel Dekker, Inc.

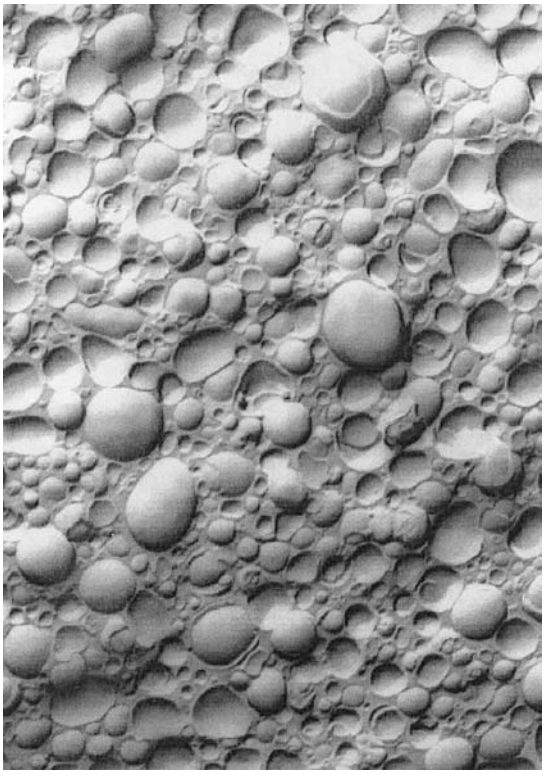


Figure 2 Freeze fracture of a liposome dispersion formed from a proliposome gel after contact with water.

C. Applications of SupraVail Vaginal Gels

Vaginal delivery systems are frequently required to treat local fungal infections, particularly candidiasis. The term "candidiasis" refers to the most common fungal infection affecting humans, and was originally ascribed to infections due to a single yeast species; *Candida albicans*. It has now been expanded to encompass a range of yeast species of the genus *Candida*. While systemic *Candida* occur, the most common *Candida* infections are superficial lesions especially of the mucous surfaces of the vagina or mouth.

Vaginal candidiasis is primarily treated with antifungal cream or pessaries inserted high into the vagina (including during menstruation). Vulvitis and superficial sites of infection can be readily treated with appropriate creams. The drugs of choice include the imidazole drugs (clotrimazole, econazole, fenticonazole,

Copyright © 2003 Marcel Dekker, Inc.

isoconazole, and miconazole) and nystatin. The poor aqueous solubility of the antifungal agents in these conventional formulations means that they are not in molecular dispersion and consequently have reduced drug concentration at the active sites. However, the poor aqueous solubility of antifungal drugs such as amphotericin, miconazole, clotrimazole, and nystatin makes them ideal candidates for SupraVail technology.

VI. DEVELOPMENT OF A SUPRAVAIL AMPHOTERICIN B GEL

A. Development

A SupraVail gel can be employed in topical drug delivery for treating mucosal fungal infections. While preliminary studies have centered on amphotericin B, it also presents as an ideal formulation for antifungal agents such as miconazole, clotrimazole, and nystatin. It consists of selected fractions of phospholipid dispersed in an anhydrous hydrophilic medium, wherein the drug is partitioned between the hydrophobic membrane lipid bilayer formed in the gel and the hydrophilic solvent phase. It confers many unique features for drug delivery to mucosal surfaces, notably:

- It is a highly efficient lipophilic carrier, utilizing natural lipid to molecularly disperse the drug. Phospholipids have natural affinity for biological membranes and are generally nontoxic and nonirritant.
- The drug is in molecular dispersion in the bilayers offering improved drug activity.
- The vehicle is nontoxic and contains pharmaceutically acceptable excipients.
- Difficulties associated with liposomal preparations, e.g., stability and loading, are circumvented because the proliposomes only convert to vesicular structures (liposomes) in vivo, i.e., on the mucosa.
- The product has a low initial microbiological burden and does not encourage microbial growth (it is preservative-free).
- SupraVail formulations can be produced on a large scale economically and reliably.
- The product is economically viable (i.e., in similar price range as current topical antifungal therapies).

B. Formulation Issues and Product Stability

A satisfactory proliposome amphotericin B gel suitable for direct application to the vaginal mucosa should take into consideration the following key factors:

Copyright © 2003 Marcel Dekker, Inc.

Stability and packaging
Drug concentration
Manufacturing method
Excipients
Antifungal activity
Release profile

1. Stability and Packaging

The stability of the drug and phospholipid components can be maximized through the selection of an appropriate hydrophilic base. Accelerated stability studies were undertaken in a variety of tube and pump packs. Accelerated stability data predicted a shelf life of 24 months at 25°C/60% relative humidity.

2. Drug Concentration

The amphotericin B concentration was 1% w/w. Greater than 95% of the drug resides in the lipid bilayers, effectively protecting the drug from degradation during storage, compared to the unprotected form.

3. Manufacturing Method

The pilot manufacturing method for producing 5 kg of the gels utilized a conventional high-shear mixer. The process may be readily scaled up for larger production batches.

4. Excipients

A number of studies were performed to assess the effects of modifying the standard proliposome gel. These included addition of antibacterial agents, antioxidants, chelating agents, and complexing agents. None of these agents (in the concentrations used) were found to alter the degradation or encapsulation profiles for the drug in the proliposome gel. The gel passes a British Pharmacopoeia (BP) microbial challenge test and was deemed to have sufficient antimicrobial activity without need for preservatives.

5. Antifungal Activity

The proliposomal amphotericin B gels demonstrated a superior antifungal activity over equivalent concentrations of drug in aqueous suspension. These findings were substantiated by growth inhibition both in solid media (cup-plate diffusion assay) and in liquid media. A comparison of the activity of amphotericin B in a SupraVail formulation against a commercially marketed product is shown in Fig-

Copyright © 2003 Marcel Dekker, Inc.

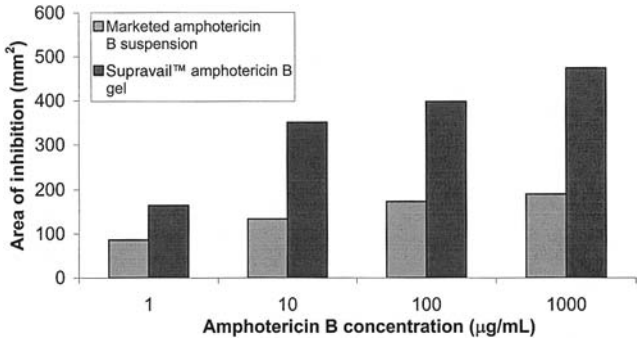


Figure 3 Comparison of antifungal activity of amphotericin B in SupraVail against commercially marketed suspension.

ure 3. The data show that higher antifungal properties were obtained with the phospholipid preparation.

6. Release Profile

The release of the drug can be controlled by altering the composition of the formulations. The release of three amphotericin B gels was determined at 37°C. It can be seen from Figure 4 that the amphotericin B can either be released immediately or more gradually, where about 40% diffuses out after 2 h.

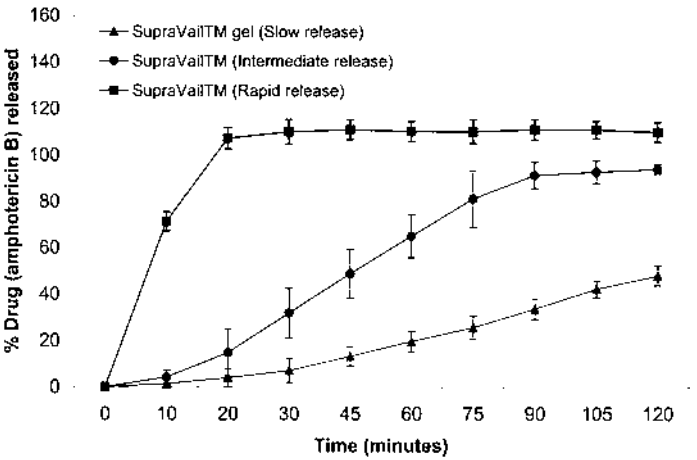


Figure 4 Release profile of amphotercin B from three SupraVail gel formulations.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Association of Drug After Conversion

Formulation	% association after conversion
1% amphotericin B	99.2
1% miconazole	97.7
1% clotrimazole	97.3

VII. DEVELOPMENT OF ALTERNATIVE ANTIFUNGAL DRUGS IN A SUPRAVAIL GEL

While amphotericin B was selected as a test model drug, development programs have also been instigated for a number of other drugs, namely clotrimazole, miconazole, and nystatin. In addition to excellent association (Table 1) and stability profiles (6 months accelerated stability data), these prototype formulations have supporting microbiological efficacy data.

VIII. REGULATORY ISSUES

While the SupraVail gel must comply with the normal demands for a standard mucocutaneous gel preparation, no specific regulatory issues arise. It should be stressed that the phospholipids used for the SupraVail gels are of exceptionally high specification and exceed the general pharmacopoeial requirements for lecithin. Certificates of analysis are issued for each of the phospholipid fractions employed, and Drug Master Files (DMFs) are available for selected fractions. Lecithin is GRAS status and would present a low toxicological challenge. While it may be necessary to perform a tolerability study for the final product (active in association with all excipients), it is believed that there would be no requirement to undertake extensive toxicological profiling of the individual formulation components.

IX. COMPETITIVE ADVANTAGE

The formulation components are readily available in bulk quantities at competitive prices and would readily lend themselves to mass marketing of competitively priced products. In addition, the manufacturing process involves standard mixing equipment and facilitates production of large-scale batches economically and reliably.

There is a potential to reduce drug dosage in these formulations. Enhanced

Copyright © 2003 Marcel Dekker, Inc.

bioavailability and drug activity have been demonstrated by presenting the drug to membranes in molecular dispersion. These formulations are also nontoxic and nonirritant and do not require the inclusion of preservatives. The gel formulations can be packaged in a number of presentations (e.g., pumps, tubes, jars).

The SupraVail gel is highly versatile and is suitable for inclusion of a number of drug compounds. While initial research has focused on the hydrophobic antifungal agents, it could be readily adapted for delivery of other actives (e.g., steroids, peptides, vaccines, and antimicrobial agents).

X. FUTURE DIRECTIONS

There is considerable promise for development and expansion of the innovative SupraVail platform technology. While vaginal delivery systems have traditionally focused on local treatment of infective and inflammatory conditions, interest has been directed on the suitability of this route for systemic delivery (e.g., peptides, vaccines, microcides, etc.). The dual-vector nature of phospholipids facilitates incorporation of both hydrophobic and hydrophilic drugs. Gels, foams, and creams can be developed and individually tailored for specific actives. The phospholipid(s) can be carefully selected and blended with actives/excipients to confer superior stability, efficacy, and patient acceptability profiles.

REFERENCES

1. GD Kobrinskii, VR Mel'nikov, VN Kulakov, ND L'vov, IM Bolotin, IF Barinskii. Treatment of experimental genital herpes with liposomal interferon, Biomed Sci 2: 29–32, 1991.
2. SK Jain, R Singh, VV Jain. Mucoadhesive liposomes bearing metronidazole for controlled and localised vaginal delivery. Proc Int Symp Control Rel Mater 23:701–702, 1996.
3. SK Jain, R Singh, B Sahu. Development of a liposome based contraceptive system for intravaginal administration of progesterone. Drug Dev Ind Pharm 23:827–830, 1997.
4. M Foldvari, A Moreland. Clinical observations with topical liposome-encapsulated interferon alpha for the treatment of genital papilloma virus infections. J Liposome Res 7:115–126, 1997.
5. Z Pavelic, N Skalko-Basnet, I Jalsenjak. Liposomes containing drugs for treatment of vaginal infections. Eur J Pharm Sci 8:345–351, 1999.
6. P Williams. Liposomes and the pro-liposome method. Seifen, Oele, Fette, Wasche (SOEFW) J 6:377–378, 1992.
7. S Perrett, M Golding, P Williams. A simple method for the preparation of liposomes for pharmaceutical applications: characterization of the liposomes. J Pharm Pharmacol 43:154–161, 1991.

Copyright © 2003 Marcel Dekker, Inc.

66
VagiSite Bioadhesive Technology

R. Saul Levinson and Daniel J. Thompson
KV Pharmaceutical Company, St. Louis, Missouri, U.S.A.

I. INTRODUCTION

Dosage form improvements that result in less frequent and more tolerable dosing regimens positively affect patient convenience, which can ultimately improve patient compliance—a key factor in a successful therapeutic outcome. The recent development of a new bioadhesive technology and its application to the treatment of vulvovaginal candidiasis (VVC) illustrates a prime example of how such advancements in dosage form technology can yield patient and therapeutic benefits.

Antifungal agents for VVC were first developed exclusively as topical products requiring successive daily applications, mainly at bedtime. Although the benefits of topical preparations for the treatment of VVC are clear, the dosing regimens and properties of conventional creams have proved to be inconvenient and messy.

II. DESCRIPTION OF TECHNOLOGY

An example of a dosage form improvement utilizing the VagiSite® bioadhesive technology is Gynazole-1®, a controlled-release, bioadhesive vaginal cream containing 2% butoconazole nitrate, marketed by Ther-Rx Corporation, St. Louis, Missouri. Gynazole-1® was developed and patented by KV Pharmaceutical Company, St. Louis, Missouri. The technology is covered by a variety of U.S. patents [1–5]. VagiSite™ is one of several bioadhesive technologies for different routes of administration that have been developed by KV. The VagiSite™ technology comprises a high-internal-phase-ratio, water-in-oil emulsion. As such, the internal

Copyright © 2003 Marcel Dekker, Inc.

phase of the emulsion acts as the carrier of the active drug (in the case of Gynazole-1® the active is butoconazole nitrate, 2%). The drug-laden internal-dispersed phase globules serve a dual purpose for both the sequestering and the controlled release of the active agent, butoconazole nitrate. The high-internal-phase-ratio emulsion containing dispersed phase globules develops a high affinity for surfaces, especially mucosal tissues. After introduction of the drug-containing emulsion to a mucosal surface, in this case the vaginal mucosa, a thin bioadhesive film of contiguous drug-laden internal-phase globules forms on the mucosal surface. This tenacious, bioadhesive film then acts as a drug delivery platform providing a controlled release of butoconazole nitrate into the lumen of the vaginal canal.

Interestingly, the process of bioadhesion is not affected by the presence of moisture; the drug delivery film actually forms on wet tissue. Furthermore, the drug delivery platform remains intact and functional for approximately 4.5 days rather than for only a few hours as seen with conventional nonbioadhesive creams and ointments [6]. By incorporating bioadhesion and the controlled release of the active agent, butoconazole nitrate present in the formulated emulsion, Gynazole-1® is able to continue the release of the active antifungal over several days, after a single dose application.

For the patient, Gynazole-1® has two distinct advantages: (a) minimization of leakage, which often occurs with conventional vaginal creams and ointments that are dosed repetitively, and (b) a desirable option to administer the medication day or night is made available because of minimal product leakage.

III. PHARMACOLOGICAL CONSIDERATIONS

A basic tenet of pharmacology is that an increased dose often yields increased adverse effects. In the case of topical vaginal preparations, such as the creams and ointments used to treat VVC, an increase in the amount of drug exposed to the living tissues can be expected to cause a greater incidence of adverse effects such as irritation, burning, and discomfort. In contrast, a single dose of Gynazole-1® accomplishes a therapeutic response equivalent to the response seen with multiple-dose products because of its bioadhesive and controlled-release properties. A dramatic "drug sparing" effect, due to the controlled release of the active agent, is observed if one notes that a single dose of Gynazole-1® contains 5.0 g of 2.0% butoconazole nitrate (a total of 100 mg of drug). Comparing this to the amount of drug delivered over 3 days with the conventional butoconazole nitrate product currently marketed (FemStat-3®), a total of 15 g of formulated product is introduced intravaginally to deliver a total of 300 mg of butoconazole nitrate. The drug-sparing effect becomes even more dramatic when compared to topical vaginal antifungals dosed longer than 3 days. (Note that head-to-head studies of

Copyright © 2003 Marcel Dekker, Inc.

Gynazole-1® and FemStat-3® have not been conducted to confirm any difference in the nature or incidence of side effects or comparability of clinical response.)

IV. CLINICAL EVALUATION

In vitro analysis of the controlled-release formulation of butoconazole nitrate in Gynazole-1® revealed continuous and slow release of active ingredient while shaken in a pH 4.3 acetate buffer. The active ingredient was released continuously from Gynazole-1® throughout a 7-day study period (Fig. 1) [6]. In contrast, a conventional marketed vaginal cream containing the same active ingredient, butoconazole nitrate, rapidly disintegrated and began to release its active drug immediately (Fig. 1) [7]. This illustrates the dramatic disparity in the delivery of active drug dependent on the emulsion system used. As a result of Gynazole-1®'s unique bioadhesive cream, it is the only one-dose vaginal cream available on the market for the treatment of VVC that can be administered anytime day or night.

The bioadhesive properties of Gynazole-1® have been clinically demonstrated in two separate studies. In the first clinical study, Weinstein et al. studied the vaginal retention time of both Gynazole-1® and a standard vaginal cream containing butoconazole nitrate 2% [6]. Sixteen healthy women were treated intravaginally with either the standard cream or the controlled release Gynazole-1® and monitored daily over 7 days. The amount of cream excreted and captured in feminine minipads was monitored for the 7 days. Analysis of the data demonstrated a median vaginal retention time of approximately 2.5 days for the standard

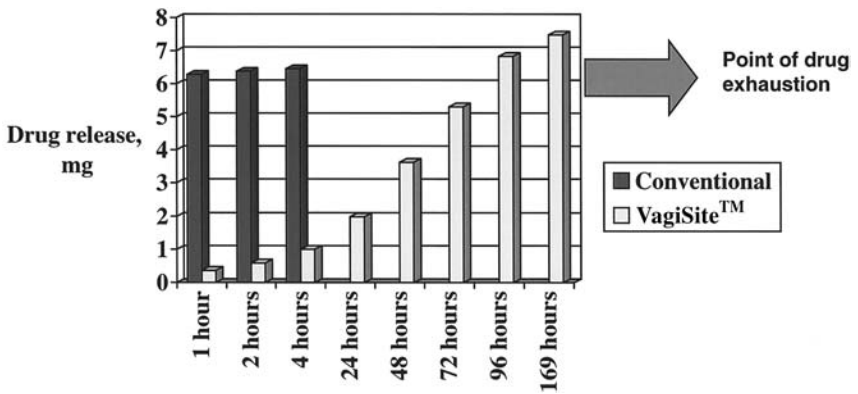


Figure 1 In vitro release of butoconazole nitrate from the Gynazole-1 VagiSite™ formulation versus a standard cream formulation containing the same active ingredient. (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Efficacy of Gynazole-1® Single-Day Treatment Versus Miconazole 7-Day Treatment

Cure rate	Treatment group		p*
	Gynazole-1®	Miconazole 7	
1st clinical follow-up: number of patients treated/cured (%)	101/93 (92)	104/100 (96)	0.24
2nd clinical follow-up: number of patients treated/cured (%)	84/74 (88)	93/80 (86)	0.92
1st microbiological follow-up: number of patients treated/cured (%)	98/85 (87)	101/93 (92)	0.75
2nd microbiological follow-up: number of patients treated/cured (%)	77/57 (74)	87/67 (77)	0.24

* p value of treatment differences between the two groups. Note that no significant difference exists.

cream. The median vaginal retention time of Gynazole-1®-treated patients was 4.2 days ($p = 0.0024$) [6]. These data demonstrate that Gynazole-1® remained intact in the vagina 63% longer than a standard formulation with the same active ingredient, butoconazole nitrate. From a therapeutic standpoint, the bioadhesive properties of Gynazole-1® enable a one-time dosing.

In the second study to reinforce the clinical attributes of the bioadhesive formulation, Brown et al. confirmed the efficacy of both Gynazole-1® and miconazole 7 when studied in 205 infected patients [8]. All 205 patients were confirmed both clinically and by potassium hydroxide smear to have vulvovaginal candidiasis. The clinical cure rates at 7–10 days post therapy initiation were comparable between Gynazole-1® and miconazole 7 at 92% and 96%, respectively (Table 1). There was no statistical difference in the clinical cure rates between the two therapies. Similarly, 30 days after treatment completion, clinical cure rates were 88% and 86% for Gynazole-1® and miconazole 7, respectively (Table 1). The microbiological cure rates were also comparable between therapies at both the initial follow-up and 30-day follow-up visits.

V. OTHER DRUG APPLICATIONS

The unique bioadhesive technology of the VagiSite™ emulsion is not limited to a formulation containing butoconazole nitrate. Ongoing internal studies have measured the bioadhesive properties of the VagiSite™ technology with those of other topical medications. In one such study, 44 healthy volunteers were enrolled in a parallel double-blind study to determine the vaginal retention time of a for-

Copyright © 2003 Marcel Dekker, Inc.

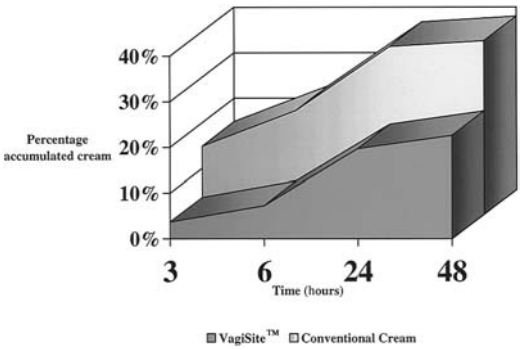


Figure 2 Percentage of accumulated cream in sanitary pads following vaginal application of equivalent doses of conventional cream versus VagiSite™ cream captured at different time intervals (3, 6, 24, and 48 h) in healthy volunteers. At all time intervals, the differences are statistically significant ($p < 0.05$). (See color insert.)

mulated antifungal in the VagiSite™ emulsion against a comparable antifungal in a standard commercial formulation. Women were given a single application of one of the two formulations. Subjects were provided sanitary pads during the course of the 48-h multipoint analysis. The returned sanitary pads were assayed using high-performance liquid chromatography methodology for detectable drug content. The VagiSite™ formulation containing active drug yielded approximately 50% of the product leakage found with the standard cream formulation (Fig. 2) [7].

VI. CONCLUSION

Efficacy data suggest that a single-dose bioadhesive topical cream formulation of butoconazole nitrate (Gynazole-1®) that utilizes the VagiSite™ bioadhesive technology is as efficacious as a multiple-dose conventional cream. VagiSite™ bioadhesive technology is a patented high-internal-phase emulsion. The technology offers sustained release and long retention times in the vagina and appears appropriate for a variety of active compounds.

REFERENCES

1. R Cuca. Stable high internal phase ratio topical emulsions. US patent 4,384,049, 1981.

Copyright © 2003 Marcel Dekker, Inc.

2. T Riley, C Tharp, G Lapka. Vaginal delivery systems and their methods of preparation and use. US patent 4,551,148, 1988.
3. T Riley. Solid controlled release bioadherent emulsions. US patent 5,055,303, 1991.
4. T Riley. Vaginal delivery system. US patent 5,266,329, 1993.
5. R Cuca, K Lienhop, T Riley, RS Levinson, M Kirschner. Improved bioadhesive delivery system. US patent 5,554,380, 1996.
6. L Weinstein, MR Henzel, IW Tsina. Vaginal retention of 2% butoconazole nitrate cream: comparison of a standard and a sustained release preparation. Clin Ther 16: 930–934, 1994.
7. Data on file, KV Pharmaceutical Company, St. Louis, Missouri 63144.
8. D Brown, MR Henzel, RH Kaufman, and the Gynazole-1 Study Group. Butoconazole nitrate 2% for vulvovaginal candidiasis: new single-dose vaginal cream formulation versus seven-day treatment with miconazole nitrate. J Reprod Med 44:933–938, 1999.

Copyright © 2003 Marcel Dekker, Inc.

67

Pulmonary Delivery of Drugs by Inhalation

Igor Gonda and Jeff Schuster
Aradigm Corporation, Hayward, California, U.S.A.

I. INTRODUCTION

This section of the book contains chapters describing various systems, devices, formulations, and methods of delivery of drugs to the lung for the treatment of diseases of the respiratory tract, or for systemic delivery via the lung. It differs somewhat from other sections in this book: it was the opinion of the editors that pulmonary delivery in general represented "modified-release technology," even though the focus is not on the control of release of the medicaments once they are deposited within the respiratory tract (although some chapters in this section do describe such approaches). It is the ability of inhalation systems to deliver drugs almost instantaneously to the target organ, which is the "release" part for therapeutic activity for many of the currently approved products for inhalation. Further, the lung provides a promising portal for noninvasive delivery of drugs to the blood and lymphatic circulation. This facilitates absorption of drugs with slow or incomplete oral bioavailability.

This section includes some general chapters [regulatory aspects (Rosario and Otulana), small molecule (Hickey), and protein powders for inhalation (Chan)]. Some chapters are primarily dedicated to already approved systems, e.g., dry powder inhalers (Ashurst and Malton), metered-dose inhalers (Adjei), and nebulizers (Knoch and Finlay). In addition, extensive reviews are included of emerging pulmonary delivery technologies, especially those that are currently being evaluated in human clinical trials [described in the chapters from Aerogen (Uster), Alkermes (Batycky et al.), Aradigm (Schuster and Farr), Boehringer Ingelheim (Zierenberg and Eicher), Dura/Elan (Witham and Phillips), and Inhale

Copyright © 2003 Marcel Dekker, Inc.

(Clark)]. This combination of chapters makes for an interesting overview of current technologies in this area.

II. BASIC PRINCIPLES

The deposition of inhaled particles in the human respiratory tract depends critically on the particle properties and the way the patients breathe at the time of delivery [1,2]. Further, since inhalation of an aerosol cloud is essentially done as volumetric filling of the lung with a mixture of air and particles, it is important for lung delivery to actuate the aerosol administration early in the breath and continue breathing until the drug aerosol has entered into the small airways and alveoli as the therapeutic needs may require.

The important "size" characteristic for deposition is called aerodynamic diameter: it is determined by the actual size of the particle, its shape, and its density. Numerous studies (reviewed in Refs. [1–3]) show that a fraction of particles in the aerodynamic size range of approximately 3.5–6 μm can penetrate to some extent at slow inspiratory flow rates beyond the central airways into the peripheral region of the lung, while particles less than 3.5 μm and greater than approximately 0.5 μm will largely bypass the bronchial airways during inhalation and penetrate almost entirely to the "deep" lung. Larger particles are dominated by their inertial mass and will impact in upper airways due to their inertia. This impaction is exacerbated by higher inhalation flow rates, and even at controlled inhalation flow, oropharyngeal deposition shows very high levels of inter- and intrasubject variability [4]. Smaller particles (aerodynamic diameter < 0.5 μm) are dominated by thermal interactions with the air molecules and will diffuse to the respiratory tract surfaces during inhalation. However, the generation of such small particles has not been possible for commercial application (of course, molecular-size gases are used as inhalational anesthetics but typical therapeutic drugs do not exist as gases or vapors at ordinary atmospheric conditions). Inspired particles larger than approximately 1 μm will deposit by gravitational sedimentation during a modest breath-holding period of 10 s or less [5]. Thus, efficient, reproducible delivery of pharmaceutical aerosols requires administration of 1–3.5 μm (aerodynamic size) particles early in the breath followed by a deep inhalation at a low, controlled inhalation flow rate. This type of controlled delivery is especially important if the target is the small airways and alveoli. A short period of breath holding is usually required to enhance deposition by sedimentation and diffusion and thus to prevent exhalation of the small particles.

Diseases of the respiratory tract affect the regional doses of inhaled drugs. Aerosols can enter only those parts of the respiratory tract that are ventilated. Particles and droplets can get past partial obstructions in airways but with enhanced deposition in the vicinity of the obstruction [6]. Reversible obstruction,

Copyright © 2003 Marcel Dekker, Inc.

such as an acute bronchoconstriction in a patient with asthma, may cause problems with intrasubject reproducibility of delivery.

The effect of hygroscopic growth further complicates the delivery of many compounds. Initially dry 1–3.5 μm hygroscopic aerosol powders may take on water vapor over a wide range of ambient conditions and grow to a diameter outside the optimum size range during inhalation [7]. Similarly, aqueous solution aerosols will evaporate and become smaller at most ambient conditions, but at relative humidities close to saturation, they can grow [8].

III. CONVENTIONAL METHODS OF INHALATION DELIVERY FOR THE TREATMENT OF RESPIRATORY DISEASE

Delivery of drugs by inhalation has become the favored route of administration for the treatment of the majority of patients suffering from respiratory diseases such as asthma, chronic bronchitis, and cystic fibrosis [9]. Obviously a significant therapeutic advantage is gained by generating high drug concentrations in the target organ, and thereby minimizing systemic exposure and the possibility of unwanted reactions in other parts of the body. Some drugs that are given by inhalation have very low oral bioavailability, and to make them effective in the respiratory tract noninvasively, they must be given by inhalation. At the time of this writing, the only protein approved for treatment of lung disease by inhalation is the recombinant human deoxyribonuclease (rhDNase) for the treatment of cystic fibrosis [10]. rhDNase would not diffuse in adequate quantities into the airways from the bloodstream even if it was administered by injection. Inhalational drug delivery has an additional advantage in that a rapid onset of action in the respiratory tract can be achieved since the surface of the lung can be, in principle, accessed by the drug in a single breath.

A variety of methods have been used to deliver respiratory drugs by inhalation. The conventional inhalation systems are designed primarily to generate particles of size suitable for topical delivery to the airways.

A. Pressurized Metered-Dose Inhalers (MDIs or pMDIs)

The most popular delivery system is the pressurized metered-dose inhaler (see chapter by Adjei). This delivery system was developed initially using chlorofluorocarbon (CFC) propellants. The drug can be present as a suspension or solution in the propellant. Special excipients that stabilize the physical state of the suspension, or enhance the drug solubility, are typically used. Because of their adverse impact on the atmospheric ozone, CFCs are being phased out. Reformulation of MDIs with alternative propellants has been challenging as they have quite differ-

Copyright © 2003 Marcel Dekker, Inc.

ent physicochemical properties compared to CFCs. These reformulations necessitated extensive investigation of new materials required for the plastic parts of MDIs as well as to replace the excipients that were compatible with CFCs but not with the alternative propellants.

Conventional MDIs produce fast-moving large droplets that need time and distance to slow down, evaporate, or break up into smaller particles. Further, the actuation of the aerosol delivery needs to be synchronized with inspiration—a maneuver that not all patients find easy to master. "Spacers" and "holding chambers" have therefore been developed to allow for some particle size reduction and to reduce the need for synchronization of the aerosol actuation with the beginning of inspiration [11].

B. Dry Powder Inhalers (DPIs)

The second most common type of inhalation systems are dry powder inhalers (see the chapter by Ashurst and Malton). In contrast to MDIs in which the fundamental aerosol generating part of the "device" is quite generic (but the formulations for different products vary), many different DPIs have been invented. These vary in the types of formulations and dosage forms they utilize as well as in the means of dispersion of the powder formulation. Indeed, formulations that may work well in one type of device could be quite ineffective in another one.

The classic DPIs are "breath-actuated." Thus, the problem of synchronization of aerosol generation with the start of inhalation does not exist. However, the energy to mobilize the powder bed, entrain it into the airstream, and break up the powder formulations into small particles is derived from the patient's breathing (these are called "passive" DPIs). Hence, the performance of these DPIs (emitted dose and its particle size distribution) does depend on the patient's technique and ability to inhale sufficient volume of air at an adequate inspiratory flow rate. More recently, "active" DPIs entered into development. Such devices utilize some form of stored energy, such as batteries or compressed air, to aerosolize the powder, with the view to eliminate the dependence of the emitted dose and particle size distribution on the patient's effort. However, it needs to be remembered that the regional distribution of the drug in the respiratory tract depends on the inspiratory flow rate and inspired volume, even if the generated dose and its particle size distribution remain constant [12].

Small molecules can be prepared as respirable-size powders using conventional manufacturing methods, such as micronization using jet milling, or spray drying (see chapters by Hickey and by Witham and Phillips). These may then be blended with large carrier particles to improve powder flow and dispersion, or turned into dispersible "snowballs" that reduce the adhesive properties of the constituent fine-drug particles. Protein drugs generally require excipients for stabilization; the preparation of physically and chemically stable respirable powders

Copyright © 2003 Marcel Dekker, Inc.

containing proteins with excipients deemed to be safe has been an area of intense academic and industrial research (see the chapter by Chan).

C. Nebulizers

The third type of pulmonary delivery systems in common use are those that aerosolize aqueous solutions of water-soluble drugs, or suspensions and solvent-water-based solutions of water-insoluble substances (see chapter by Knoch and Finlay). These are jet and ultrasonic nebulizers. In contrast to MDIs and DPIs which are hand-held products that deliver the required dose in one, or a small number, of inhalations, traditional nebulizers are not easily portable and the dose administration typically takes more than 10–15 min. However, some drugs are only available as solutions for nebulization, and certain patient populations, especially small children, may not be able to use any other means of aerosol delivery.

Nebulizers typically employ liquid formulations that are ready to use by the patient. Sometimes isotonic saline is added for dilution. It is preferable to use simple formulations (drug dissolved in water) to avoid potential adverse reactions with preservatives and other excipients. In fact, the new regulation in the United States, which came into force in 2002, requires that all inhalation solutions for nebulization be sterile (see the chapter by Rosario and Otulana), thus eliminating the need for preservatives in these products (as long as they are presented in single-use containers). The lung, of course, is an external organ open constantly to the environment, so the aerosol generation system, or the aerosol inhaled by the patient, does not need to be sterile. The requirement of sterility of the solution at the time of manufacture protects the product against degradation and buildup of potentially hazardous levels of microorganisms in the formulation upon storage. Interestingly rhDNase (see above) is presented in a single-use vial containing a sterile aqueous solution of the protein molecule with saline to adjust the tonicity and a small quantity of calcium chloride for stability of the protein [10]. While aqueous solutions of biologics may not have long-term room temperature stability, they afford a simple, economic path to product development leveraging the experience with the low-risk excipient—water. This factor has been a key impetus to develop modern highly efficient, reproducible, and hand-held systems for aerosolization of aqueous solutions (see the chapters by Knoch and Finlay, Uster, Zierenberg and Eicher, and Schuster and Farr).

IV. BEYOND THE CONVENTIONAL DELIVERY OF RESPIRATORY DRUGS

The majority of patients currently use the small, pocket-size MDIs or DPIs because of their convenience and low cost. Classic asthma drugs are small mole-

Copyright © 2003 Marcel Dekker, Inc.

cules with a relatively wide safety margin. For example, bronchodilators are typically administered at the top of the dose-response curve and therefore the efficiency and reproducibility of delivery are not critical. Indeed, many studies have shown that the majority of patients cannot use these devices correctly without frequent coaching by qualified health care professionals (reviewed in Ref. [13]). The breathing technique in particular is a major cause of inefficient and variable delivery.

The announcement of the phaseout of CFCs was a strong impetus for intensive research and development of alternative delivery systems. Additionally, the growth of protein, peptide, and gene medicines that are not absorbed from the gastrointestinal tract prompted the exploration of the pulmonary route for their systemic delivery [9]. Efficiency of pulmonary delivery of biologics is an important economic issue because of the relatively high cost of producing them and the complexity of their quality control. Pulmonary delivery systems until recently have been typically delivering only 10–20% of the available drug to the lung, with high coefficients of variations, (e.g., >60% for MDIs [14]). Over the last decade, significant improvements have been made to the efficiency and precision of pulmonary drug delivery. The general trends are summarized in Table 1.

The lung presents a very attractive route for the noninvasive delivery of systemically active compounds. The large surface area coupled with the very thin epithelium and highly vascularized nature of the pulmonary region of the lung, optimized for the efficient exchange of oxygen and carbon dioxide between the circulatory system and inhalation air, can be utilized as a "portal of entry" for the delivery of medication. However, the bronchial airways, in addition to being a distribution system of inhaled air to the pulmonary region, are also a highly evolved filter for removing particles from inhaled air and clearing them from the lung. Efficient delivery to the systemic circulation requires particles small enough to bypass this filter.

Table 1 General Trends and Improvements to the Efficiency and Precision of Systemic Delivery of Drugs via the Lung

Development of pulmonary delivery technology		
Chlorofluorocarbon propellant-driven metered-dose inhalers	⟶	Interim HFA solution, followed by "soft mists"?
No breath control	⟶	Device-assisted breath control
Patient effort-dependent drug delivery from dry powder inhalers	⟶	Power-assisted devices, smart formulations
Patient education	⟶	Smart devices
Pharmacokinetic/pharmacodynamics determined by drug properties	⟶	Pharmacokinetic/pharmacodynamics determined by delivery: formulation, device

Copyright © 2003 Marcel Dekker, Inc.

The majority of products currently in development for systemic administration via the lung contain drugs that are already approved for use by parenteral administration, such as insulin for the treatment of type 1 and type 2 diabetes (see Refs. [15] and [16] as well as the chapters by Clark and by Schuster and Farr), and morphine or fentanyl for the treatment of breakthrough pain [17,18]. There are obvious convenience and safety benefits to patients resulting from noninvasive delivery via the pulmonary route. It is anticipated that the ease of administration will improve quality of life, and compliance with the optimum therapeutic regimen. For comparable safety and efficacy, it is also expected that the reproducibility of the pharmacokinetics and pharmacodynamic effects following pulmonary administration will need to be comparable to that obtained with parenteral administration. It is therefore not surprising that the most advanced pulmonary delivery systems that are being developed for systemic delivery of drugs incorporate elements that attempt to improve on the reproducibility of the conventional aerosol generators (CFC MDIs, asthma DPIs and nebulizers). The aerodynamic size range suitable for deep lung delivery and adequate management of the patient's technique during the dosing (inspiratory flow rate, delivery early in the inspiration, total inhaled volume for some drugs such as insulin [19]) are the critical factors affecting the absorption of inhaled drugs.

V. MODIFIED-RELEASE FORMULATIONS FOR PULMONARY DELIVERY

There has been sporadic interest in the development of controlled-release formulations for inhaled drugs for local treatment of pulmonary disease. The problem is quite complex because different parts of the respiratory tract are cleared by different mechanisms [20]. The residence time of the drug in various parts of the respiratory tract as it is released from particles and droplets is therefore affected not only by the nature of the formulation, but also by the ability of the mucociliary escalator and macrophages to remove such "foreign matter" from the conducting airways and alveoli, respectively. Further, since the therapeutic effects of the drug in the respiratory tract are presumably related to the drug released from the controlled-release carrier, the right balance between the rate of release and rate of clearance from the lung has to be found [20]. Finally, the disparity in the rate of clearance of the carrier material and the active component needs to be taken into account to prevent undesirable accumulation of such carriers in the respiratory tract.

VI. CONCLUSIONS

Pulmonary delivery systems have undergone tremendous evolution over the last few decades. A wide variety of particles and droplets have been engineered to

Copyright © 2003 Marcel Dekker, Inc.

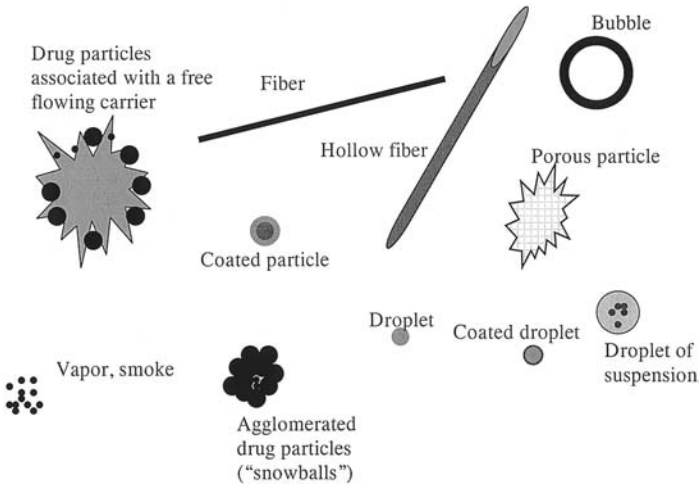


Figure 1 Schematic diagram of particles and droplets that have been engineered to achieve effective deposition in the desired regions of the respiratory tract to provide the means for modulated release following deposition.

achieve effective deposition in the desired regions of the respiratory tract. Some interesting work has been done to produce particles and droplets to provide the means for modulated release following deposition (Fig. 1). The trend (Table 1) is to shift away from aerosol generators that deliver a large fraction of the drug dose to the oropharynx, causing high variability of delivery to the lung, to systems with smaller particles and low-velocity clouds. Many of the new designs have features designed to minimize the potential for incorrect technique to affect pulmonary delivery.

REFERENCES

1. I Gonda. Targeting by deposition. In: AJ Hickey, ed. Pharmaceutical Inhalation Aerosol Technology. New York: Marcel Dekker, 1992, pp. 61–82.
2. I Gonda. Physico-chemical principles in aerosol delivery. In: DJA Crommelin, KK Middha, eds. Topics in Pharmaceutical Sciences 1991. Stuttgart: Medpharm Scientific Publishers, 1992, Chapter 7, pp. 95–115.
3. I Gonda. Particle deposition in the human respiratory tract. In: RG Crystal, JB West, eds. The Lung: Scientific Foundations. 2nd ed. Philadelphia: Lippincott-Raven Publishers, 1997, Chapter 176, pp. 2289–2294.
4. PE Morrow, CP Yu. Models of aerosol behavior in airways. In: F Moren, MT Newhouse, MB Dolovich, eds. Aerosols in Medicine. Amsterdam: Elsevier, 1985, pp. 149–191.

Copyright © 2003 Marcel Dekker, Inc.

5. ED Palmes, B Altshuler, N Nelson. Deposition of aerosols in the human respiratory tract during breath holding. In: CN Davies, ed. Inhaled Particles and Vapours II. New York: Pergamon Press, 1967, pp. 339–349.
6. WD Christensen, DL Swift. Aerosol deposition and flow limitation in a compliant tube. J Appl Physiol 60:630–637, 1986.
7. I Gonda, JB Kayes, CV Groom, FJT Fildes. Characterisation of hygroscopic inhalation aerosols. In: N Stanley-Wood, T Allen, eds. Particle Size Analysis. London: Heyden, 1982, pp. 31–43.
8. PR Phipps, I Gonda, SD Anderson, D Bailey, G Bautovich. Regional deposition of saline aerosols of different tonicities in normal and asthmatic subjects. Eur Respir J 7:1474–1482, 1994.
9. I Gonda. The ascent of pulmonary drug delivery. J Pharm Sci 89:940–945, 2000.
10. I Gonda. Deoxyribonuclease inhalation. In: AL Adjei, PR Gupta, eds. Inhalation Delivery of Therapeutic Peptides and Proteins. New York: Marcel Dekker, 1997, Chapter 12, pp. 355–365.
11. RN Dalby, SL Tiano, AJ Hickey. Medical devices for the delivery of therapeutic aerosols to the lung. In: AJ Hickey, ed. Inhalation Aerosols: Physical and Biological Basis for Therapy. New York: Marcel Dekker, 1996, Chapter 14, pp. 441–473.
12. SJ Farr, AM Rowe, R Rubsamen, G Taylor. Aerosol deposition in the human lung following administration from a microprocessor controlled pressurised metered dose inhaler. Thorax 50:639–644, 1995.
13. R Rubsamen. Novel aerosol peptide drug delivery systems. In: AL Adjei, PK Gupta, eds. Inhalation Delivery of Therapeutic Peptides and Proteins. New York: Marcel Dekker, 1997, Chapter 24, pp. 703–731.
14. L Borgström, L Asking, O Beckman, E Bondesson, A Källén, B Olsson. Discrepancy between in vitro and in vivo dose variability for a pressurized metered dose inhaler and a dry powder inhaler. J Aerosol Med 11(suppl 1):S59–S64, 1998.
15. M Berelowitz, G Becker. Inhaled insulin—clinical pharmacology and clinical study results. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 151–154.
16. PG Clauson, B Balent, GA Brunner, G Sendlhofer, JH Jendle, V Hatorp, UL Dahl, J Okikawa, TR Pieber. PK-PD of four different doses of pulmonary insulin delivered with the AERx diabetes management system. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 155–161.
17. EM Ward, A Woodhouse, LE Mather, SJ Farr, JK Okikawa, P Lloyd, JA Schuster, RM Rubsamen. Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. Clin Pharm Ther 62:596–609, 1997.
18. LE Mather, A Woodhouse, ME Ward, SJ Farr, RA Rubsamen, LG Elterington. Pulmonary administration of aerosolized fentanyl: pharmacokinetic analysis of systemic delivery. Br J Clin Pharmacol 46:37–43, 1998.
19. SJ Farr, A McElduff, LE Mather, J Okikawa, ME Ward, I Gonda, V Licko, RM Rubsamen. Pulmonary insulin administration using the AERx system: physiological and physicochemical factors influencing insulin effectiveness in healthy fasting volunteers. Diabetes Tech Ther 2:185–197, 2000.
20. I Gonda. Drugs administered directly into the respiratory tract: modeling of the duration of effective drug levels. J Pharm Sci 77:340–346, 1988.

Copyright © 2003 Marcel Dekker, Inc.

68

Aerogen Pulmonary Delivery Technology

Paul S. Uster
AeroGen Inc., Mountain View, California, U.S.A.

I. INTRODUCTION

AeroGen specializes in the development, manufacture, and commercialization of therapeutic pulmonary products for local and systemic disease. Drugs can be delivered via liquid aerosols to the lungs to treat local diseases such as asthma, or through the lungs to the bloodstream to treat systemic disease such as diabetes. Classic pulmonary delivery systems (nebulizers, propellant-driven metered-dose inhalers) were hampered by poor device efficiency and suboptimal lung deposition. In the past decade, new pulmonary delivery technologies have emerged to address these issues.

The technology being developed at AeroGen consists of a proprietary aerosol generator (AG) that atomizes liquids to a predetermined particle size. Existing drug formulations can be used as is, or modified in consideration of existing inhalation products outlined in the Food and Drug Administration *Inactive Ingredients Guide* [1]. Whether incorporated into a pocket-sized AeroDose™ inhaler (Fig. 1), or attached to a mechanical ventilator (AeroNeb™ inline nebulizer; Fig. 2) these delivery platforms accommodate drugs and biopharmaceuticals formulated as solutions, suspensions, colloids, or liposomes [2]. Dispensing can be from unit-dose, multidose, or patient-adjustable containers.

Copyright © 2003 Marcel Dekker, Inc.

Figure 1 AeroDose inhaler.

Figure 2 AeroNeb portable nebulizer.

Copyright © 2003 Marcel Dekker, Inc.

II. HISTORICAL DEVELOPMENT

AeroGen's scientific founder originally conceived of a broad variety of applications for a technology capable of producing fine aerosol mists of defined droplet size. Areas included energy, consumer products, and pharmaceuticals. The company incorporated in California in November 1991 under the name Fluid Propulsion Technologies, Inc. to encompass this broad scope of potential. The tremendous importance of pulmonary drug delivery created a natural focus, and in April 1997, the name was changed to AeroGen, Inc.

III. PATENT INFORMATION/STATUS

Seminal patents and patent applications describe the novel and useful methods and apparatus by which a precise and fine liquid aerosol is produced as an atomized spray. In one exemplary embodiment, the apparatus comprises a thin shell member having a front surface, a rear surface, and a plurality of tapered apertures extending between them. The apertures are tapered to narrow from the rear surface to the front surface. Predetermined volumes of liquid are supplied to the rear surface, and the nonplanar member is vibrated at high frequency to eject liquid droplets from the front surface of the thin shell member [3,4] The apparatus may optionally include a breath sensor, which detects the patient's inspiratory flow rate and transmits a signal to activate the aerosol spray [5]. Likewise, the liquid-dispensing mechanisms, which provide dosage format flexibility, are patented for liquids [6] and reconstitutable powders [7]. Additional patents and patent applications are in process.

IV. TECHNOLOGY NICHE

The technology naturally lends itself to pediatric and geriatric patients who are unable to use metered-dose inhalers (MDI) because of breath coordination issues. Patients on mechanical ventilation also cannot be treated with dry powder inhaler technologies and are suited for AeroGen technology.

V. RESPIRATORY PROGRAM

AeroGen is building a respiratory products portfolio. Roughly half of all cystic fibrosis patients, chronic obstructive pulmonary disease patients, and asthmatics

Copyright © 2003 Marcel Dekker, Inc.

(infant to 6 years old) use nebulizer devices.* Pediatric (0–6 years old) asthma prevalence was projected at 2.9 million patients in 2000–2001.†

Classic nebulizer technology is bulky, awkward to use, noisy, time-consuming, and inconvenient. The initial products will focus on treating asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). They are intended to improve treatment for patients currently using nebulizers and those receiving therapy via ventilators. One example is the development with Chiron Corporation of a small, handheld AeroDose inhaler to deliver TOBI®, an inhaled tobramycin treatment for CF.

VI. SYSTEMIC DELIVERY OF DRUGS AND BIOPHARMACEUTICALS

The technology lends itself to systemic drug delivery because of the precise aerosol control and high device efficiency. The first such product in development is an AeroDose inhaler delivering insulin to treat diabetes. The initial clinical trial for this product has been completed, and more studies in the United States and Europe are in progress.

VII. COMPARISONS/CONTRASTS WITH OTHER PULMONARY DELIVERY TECHNOLOGIES

MDIs are propellant-driven and produce a high-velocity, coarse spray. AeroGen technologies produce a low-velocity, highly respirable aerosol that improves lung deposition of respiratory drugs and biopharmaceuticals [8]. Propellants are not used, so there is no "icy back-of-the-mouth" taste. One AeroGen inhaler can handle several medications, and breath coordination is not needed. Natural breathing patterns, even with interrupted breathing or coughing, are accommodated with the inhaler's inspiratory flow-sensing mechanism.

Conventional nebulizers are generally of considerable size and weight, are noisy, and are not very portable. Aerosol droplet size distributions of nebulizers tend to be large and coarse, and are not suitable for systemic delivery applications. Considerable medication is left in nebulizers, and the medication is concentrated in that wasted volume. AeroGen technology and dispensing systems eliminate these issues. The result is improved device efficiency, markedly shorter dosing periods, and better dosimetry. AeroGen technology is ideal for macromolecules [2], as there as there is reduced waste and no shear effects or heating that lead to inactivation.

---

* Source: Audit of Intended Drug Uses by Diagnosis, 1998.

† Source: MMWR, NIH, Self-reported Asthma Survey, 1995.

Copyright © 2003 Marcel Dekker, Inc.

Many of the emerging delivery technologies use proprietary unit dosage formats, such as blister packs. The formulation flexibility of the AeroGen systems enables existing formulations to be packaged in a variety of unit-dose, multidose, or patient-adjustable container formats.

VIII. MECHANISM OF DRUG RELEASE

The aerosol generator contains a domed, or curved, plate that contains multiple holes (apertures) of a tapered shape and specified diameter (Fig. 3). The aperture plate is produced through electroforming a strong, corrosion-resistant, and durable metal alloy. The plate is placed within a circular piezoceramic element, and when energy is applied to this element, the plate vibrates. This creates a micropumping action that draws solutions in contact with the concave surface of the plate through the apertures to form a fine-particle aerosol. The aerosol particle size formed is proportional to the size and shape of the holes in the aperture plate. Thus, lung deposition (alveolar versus respiratory tree) can be controlled by selection of aperture hole diameter (down to 3 μm and less) during the manufacturing process. The aerosolization rate is generated by the micropumping action, and is controlled by programmed voltage and frequency applied to the piezoceramic element. The aerosol generator is then incorporated into AeroGen's delivery platforms, which are designed to accommodate a broad selection of dosage containers and feed systems.

IX. TECHNOLOGY RESEARCH AND DEVELOPMENT

The aerosol generator has tremendous flexibility with respect to formulation parameters such as surface tension and viscosity [9]. It accommodates actives ranging from small chemical entities to biopharmaceutical hormones, cytokines, and

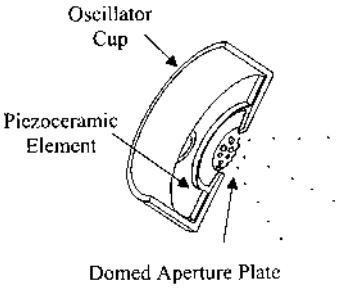


Figure 3 AeroGen's aerosol generator.

Copyright © 2003 Marcel Dekker, Inc.

immunoglobulins [2]. Device efficiencies are high, typically 80–98% of the nominal dose being emitted from the device and available for respiration. The respirable dose fraction is, of course, highly dependent on the preselected mean aerosol particle size, but fine-particle fractions (0.5–6.0 μm) as high as 90–95% have been achieved [2,10].

The aerosols show good correlation of the lung deposition predicted by computer modeling and in vitro characterization particle size distribution by laser diffraction analysis with phase I scintigraphy data [8].

Clinical proof of principle for the technology has been demonstrated in scintigraphy studies using technetium (^{99m}Tc)-spiked formulations for gamma camera imaging and quantification. In recently published work analyzing six normal volunteers given ^{99m}Tc-albuterol in the AeroDose or by an MDI, there was four times greater lung deposition (70% versus 18%) with the AeroDose [11].

Also, the AeroDose has successfully delivered biologically active insulin to the systemic circulation via the inhalation route. In a randomized, two-way crossover, euglycemic clamp clinical study, recombinant human insulin delivered by the AeroDose was compared with subcutaneous injection. The relative bioavailability and biopotency were determined from insulin concentration and glucose infusion rates, respectively. Inhaled insulin was absorbed more quickly than subcutaneous administration, which suggests the AeroDose can be an effective and needle-free method for delivering premeal insulin to diabetic patients [12].

X. FUTURE DEVELOPMENTS OF TECHNOLOGY

One interesting future application will be the incorporation of other prolonged-release drug delivery technologies into the resulting aerosols. The formulation flexibility of this particular aerosol technology lends itself to further advances in sustained and targeted drug delivery in the lung.

REFERENCES

1. Inactive Ingredients Guide. Washington, DC: Division of Drug Information Resources, Food and Drug Administration, Center for Drug Evaluation and Research, January 1996, pp. 1–155.
2. M Simon, V Gopalakrishnan. Aerodose inhaler—feasibility studies with the aerosol generator. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 311–314.
3. Y Ivri, CH Wu. Liquid dispensing apparatus and methods. US patent 5,758,637, 1998.
4. Y Ivri, CH Wu. Liquid dispensing apparatus and methods. US patent 6,085,740, 2000.

Copyright © 2003 Marcel Dekker, Inc.

5. Y Ivri, CH Wu. Apparatus and methods for the delivery of therapeutic liquids to the respiratory system. US patent 5,586,550, 1996.
6. Y Ivri. Methods and apparatus for dispensing liquids as an atomizer spray. US patent 5,938,117, 1999.
7. Y Ivri. Methods and apparatus for storing chemical compounds in a portable inhaler. US patent 6,014,970, 2000.
8. V Gopalakrishnan, CF Lange, WH Finlay. Aerodose inhaler: comparison of in vitro particle size data, computer modeled and scintigraphic lung deposition profiles. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 303–306.
9. V Gopalakrishnan, W Xia. Aerodose inhaler: effect of formulation physicochemical properties on aerosol properties. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 299–301.
10. M Simon, V Gopalakrishnan. Aerodose inhaler-aerosol characteristics of a systemic and a respiratory drug. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 307–309.
11. LR De Young, F Chambers, S Narayan, C Wu. Albuterol sulfate delivery from the aerodoseä liquid inhaler. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Hilton Head, SC: Serentec Press, 1998, pp. 315–316.
12. RS Fishman, D Guinta, F Chambers, R Quintana, DA Shapiro. Insulin administration via the aerodose inhaler: comparison to subcutaneously injected insulin. American Diabetes Association 60th Scientific Sessions, San Antonio, TX, 2000, pp. 38-OR.

Copyright © 2003 Marcel Dekker, Inc.

69

The AERx Pulmonary Drug Delivery System

Jeff Schuster and S. J. Farr
Aradigm Corporation, Hayward, California, U.S.A.

I. INTRODUCTION

Delivery of aerosolized drugs to the lungs presents significant opportunities, both for the topical treatment of lung disease and for the noninvasive delivery of systemically active compounds. Unlike other noninvasive methodologies, such as transdermal techniques, delivery via the lung takes advantage of a physiological "portal of entry" to the systemic circulation [1].

A number of constraints need to be satisfied to achieve efficient and reproducible delivery systems that comply with regulatory demands, are reasonably "patient-friendly," and are economically viable. Aradigm Corporation has been developing a family of pulmonary delivery systems [2] with these constraints in mind.

To avoid the oropharynx and more central airways, particle diameters less than approximately 3.5 μm must be generated [3]. Particle sizes can be affected by hygroscopic growth [4,5], and high relative humidity can cause significant increase in particle diameter on time scales similar to transit times for aerosols through the oropharynx and bronchial airways [6]. Efficient deposition with a minimum amount of exhaled aerosol requires particles larger than approximately 1 μm [7]. Regional deposition of aerosols is also affected by inhalation flow rate [8].

Recently, the U.S. Food and Drug Administration has mandated that liquid aerosol delivery systems utilize sterile dosage forms [9].

This chapter describes a novel unit-dose liquid aerosol delivery technology, the AERx™ system [2,10].

Copyright © 2003 Marcel Dekker, Inc.

II. THE AERx SYSTEM

The AERx aerosol drug delivery system was developed to efficiently deliver topical and systemically active compounds to the lung in a way that is independent of such factors as user technique or ambient conditions [10]. A single-use, disposable dosage form ensures sterility and robust aerosol generation. This dosage form is placed into an electronically controlled mechanical device for delivery.

III. THE AERx DOSAGE FORM

The AERx dosage form (Fig. 1) is a multilayer laminate designed to both ensure the stability of the pharmaceutical compound on storage and facilitate the robust generation of the aerosol [11]. The formulation is packaged in a blister layer consisting of polymer components that ensure stability of the pharmaceutical compound and also provide a barrier to the loss of water during storage. After the formulation is dispensed into the blister, a multilayer laminate is heat-sealed to the top of the blister. This laminate, in addition to providing the same storage and stability functions as the blister layer, also contains a single-use disposable nozzle array.

Figure 1 The AERx dosage form.

Copyright © 2003 Marcel Dekker, Inc.

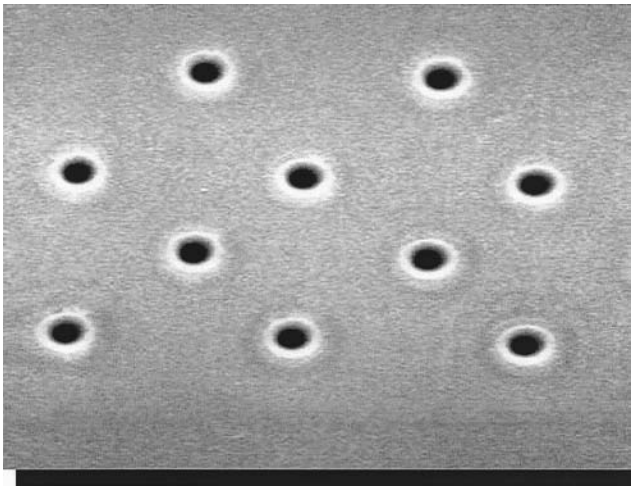


Figure 2 AERx nozzle array.

This nozzle array consists of hundreds of approximately 1-μm holes laser-micromachined into a polymer film (Fig. 2).

Prior to filling, the formulation is carefully filtered to remove particulates. This, combined with the single-use nature of the nozzle array, ensures that the aerosol generation process is not affected by nozzle blockage from particulates or dried formulation.

IV. THE AERx DEVICE

Prior to a drug delivery event, the AERx dosage form is placed into an electronically controlled mechanical device (Fig. 3). This device is battery-powered and handheld to allow complete portability. The device incorporates many features designed to eliminate possible causes of dosing irreproducibility. To eliminate variability due to uncontrolled inhalation rate, the device prompts and trains the subject to inhale at the optimal rate by presenting multicolored, flashing, and steady-light-emitting diodes. In addition to monitoring the inhalation flow rate, the device calculates an inhaled volume, and will trigger the generation of aerosol only if the inhalation rate is in the best range during a predetermined range early in the inspiration, a technique that has been previously shown to optimize lung deposition [12]. When the patient achieves this optimum flow/volume "window," an electronically controlled motor actuates a piston, which pressurizes the formu-

Copyright © 2003 Marcel Dekker, Inc.

Figure 3 The AERx device (with dosage forms).

lation blister in the dosage form. When the formulation is pressurized, the heat seal peels open in a controlled region, and the formulation flows from the blister through the nozzle array, forming an aerosol. This aerosol is entrained in the patient's inhalation air, and is delivered to the lungs.

To generate an optimal aerosol size distribution across the range of expected in-use ambient conditions, the device provides an air-temperature-controlling module [13]. This module is electrically preheated prior to the drug delivery event. During inspiration, the inhalation air is drawn through the module, warming the air. Because the air is warmed, the aerosol generation always occurs in conditions of low relative humidity, eliminating the possibility of hygroscopic growth (Tables 1 and 2).

Many optional features can be incorporated into the AERx device, depending on the requirements of the therapy. For asthma and other lung diseases, an integrated instrument has been developed to measure indicators of lung function such as peak flow or FEV_1 [14]. Compliance to critical dosing regimens can be ascertained with onboard memory that monitors time and date of dosing event, along with other required parameters. Applications, such as pain management, that require multiple doses in a short period of time with minimal patient interven-

Copyright © 2003 Marcel Dekker, Inc.

Table 1 The Effect of Ambient Conditions on Aqueous and Powder Aerosols

Aerosol	Temp. (°C)	RH (%)	MMAD (μm)	GSD	FPF
Isotonic saline [4], Hudson updraft	23–24	100	4.2 ± 0.3	1.5 ± 0.1	33%
Isotonic saline [4], Hudson updraft	23–24	65–75	2.7 ± 0.3	1.5 ± 0.1	73%
Fluorescein powder [29]	37 ± 0.1	97 ± 1	5.5 ± 0.60	1.4 ± 0.12	9%
Fluorescein powder [29]	37 ± 0.1	20 ± 5	3.8 ± 0.24	1.5 ± 0.13	42%

RH, relative humidity; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; FPF, fine-particle fraction, % <3.5 μm.

tion can be facilitated with an autoloading multidose cassette feature. Use by a nonpatient can be eliminated with a patient identification feature that disables the device until a special patient identification bracelet is placed in contact with the device.

One particularly unique feature of the AERx system is the ability to titrate fractional doses from a single dosage form [15]. This is accomplished by controlling the stroke of the piston, and retracting it when the desired dose is achieved. This feature is valuable when the dose delivered needs to be tightly controlled, and varies in time or between patients. An example is the control of diabetes with insulin [16]. The required dose can vary with such factors as measured blood glucose level, expected food intake, and body weight. Unlike any other aerosol drug delivery system, this feature allows the AERx system to deliver controlled fractions of the dosage form contents in accurate 10% increments (Fig. 4).

Table 2 The Effect of Ambient Conditions on AERx.

Temperature (°C)	RH (%)	MMAD (μm)	GSD	ED (%)	FPD (%)
40	80	2.42	1.34	72.7	65.1
40	10	2.15	1.33	75.7	72.1
22	50	2.47	1.34	77.0	67.9

RH, relative humidity; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; ED, emitted dose (as a fraction of the loaded dose); FPD, fine-particle dose (fraction of the loaded dose in particles <3.5 μm).

Copyright © 2003 Marcel Dekker, Inc.

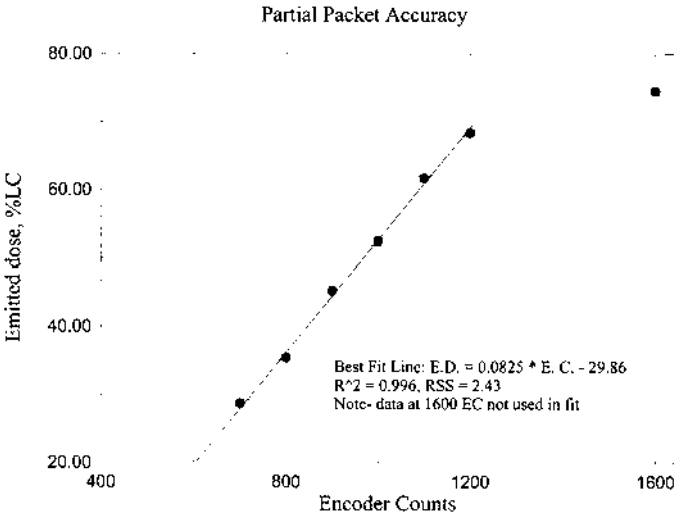


Figure 4 AERx dose titration accuracy.

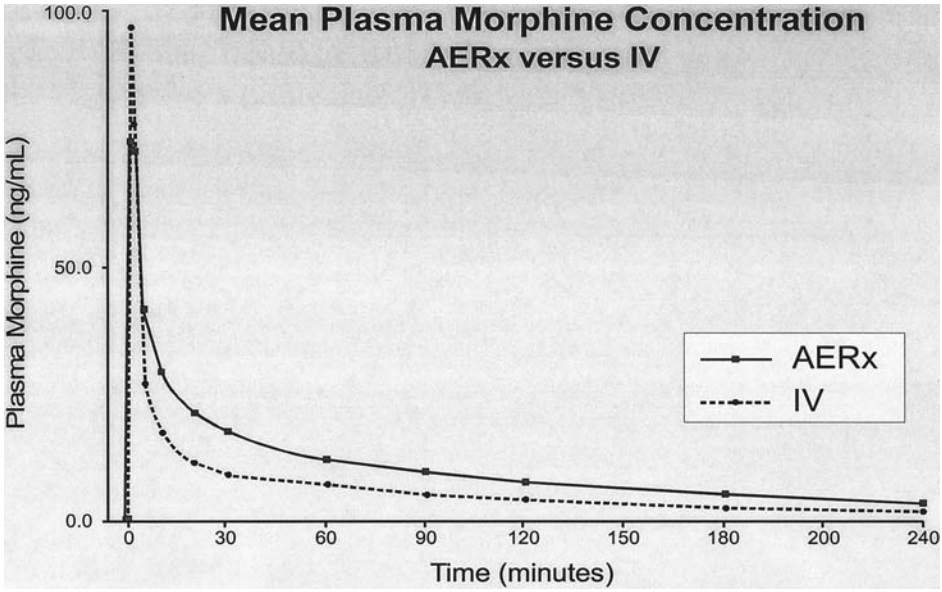


Figure 5 AERx morphine plasma concentration curve.

Copyright © 2003 Marcel Dekker, Inc.

V. CLINICAL DATA

The AERx system has been tested in the clinic with a wide variety of small-molecule [17], protein and peptide drugs [18–20], gene vectors [21], and diagnostic agents [22,23]. Pharmacokinetic studies with morphine sulfate [24,25] are illustrative of the potential capabilities of the technology. Peak plasma concentrations are achieved in less than 1 min following inhalation, and greater than 90% of the morphine emitted from the device appears in the systemic circulation. Plasma concentration profiles are indistinguishable from intravenous injection (Fig. 5).

Another well-studied application of the AERx system is delivery of human insulin for the management of diabetes [26,27]. Clinical data show that glycemic control similar to subcutaneous injection is achievable. However, minimum glycemic levels are achieved in approximately 1 h, versus approximately 2 h for a subcutaneous injection. This more rapid response is much more similar to the glucodynamics in nondiabetics, and will allow insulin dosing at mealtime, as opposed to dosing 30–60 min prior to meals as is presently required with injections. Depth of inhalation has been shown to have a significant effect on insulin

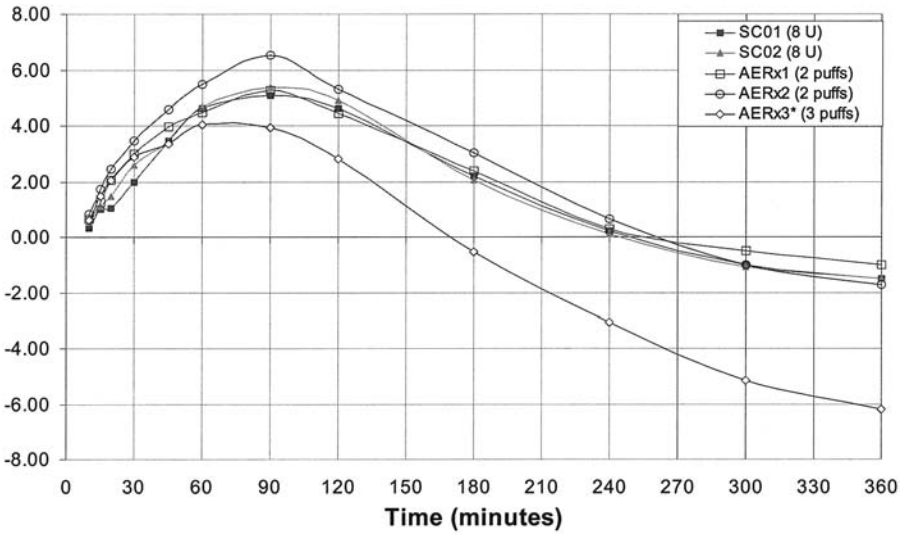


Figure 6 Glucodynamics following insulin administration with AERx.

Copyright © 2003 Marcel Dekker, Inc.

bioavailability [28], suggesting the need for breath control like that demonstrated with the AERx system (Fig. 6).

VI. CONCLUSIONS

Delivery of drugs by aerosol inhalation presents a significant opportunity for rapid, reproducible, noninvasive therapy. The AERx system takes advantage of this opportunity by optimizing aerosol characteristics and patient compliance, and by removing sensitivity to ambient conditions. Clinical data have shown that inhalation therapy is capable of reproducing, or in some cases improving on, injections.

REFERENCES

1. G Taylor. The absorption and metabolism of xenobiotics in the lung. Adv Drug Deliv Rev 5:37–61, 1990.
2. J Schuster, R Rubsamen, P Lloyd, J Lloyd. The AERX aerosol delivery system. Pharm Res 14:354–357, 1997.
3. Task Group on Lung Dynamics. Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys 12:173–207, 1966.
4. PR Phipps, I Gonda, SD Anderson, D Bailey, G Bautovich. Regional deposition of saline aerosols of different tonicities in normal and asthmatic subjects. Eur Respir J 7:1474–1482, 1994.
5. G Ferron, Kreyling, J Haider. Inhalation of salt aerosol particles. II. Growth and deposition in the human respiratory tract. J Aerosol Sci 19:611–631, 1987.
6. NA Fuchs. Evaporation and Droplet Growth in Gaseous Media. Oxford: Pergamon Press, 1962, pp. 1–37.
7. P Byron. Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J Pharm Sci 75:433–438, 1986.
8. WC Hinds. Aerosol Technology. New York: Wiley, 1982, pp. 211–231.
9. Draft Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products, Chemistry, Manufacturing and Controls Documentation. Washington, DC: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 8, 1999.
10. J Schuster, SJ Farr, D Cipolla, T Wilbanks, J Rosell, P Lloyd, I Gonda. Design and performance validation of a highly efficient and reproducible compact aerosol delivery system: AERx. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Buffalo Grove, IL: Interpharm Press, 1998, pp. 83–90.
11. SJ Farr, J Schuster, J Lloyd, P Lloyd, J Okikawa. R Rubsamen. AERx—development of a novel liquid aerosol delivery system: concept to clinic. In: I RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Buffalo Grove, IL: Interpharm Press, 1996, pp. 175–185.

Copyright © 2003 Marcel Dekker, Inc.

12. SJ Farr, A Rowe, R Rubsamen, G Taylor. Aerosol deposition in the human lung following administration from a microprocessor-controlled pressurised metered-dose inhalaer. Thorax 50:639–644, 1995.
13. J Schuster, G McKinley, P Lloyd, Igor Gonda. Developing systems for aerosol drug delivery that are independent of ambient conditions. Abstracts of the Aerosol Societies Drug Delivery to the Lungs X, London, 1999, pp. 147–150.
14. I Gonda, J Schuster, R Rubsamen, P Lloyd, D Cipolla, SJ Farr. Inhalation delivery systems with compliance and disease management capabilities. J Control Rel 53: 269–274, 1998.
15. J Schuster, D. Hasegawa. Dose titration with the AERx system. Abstracts of the Aerosol Societies Drug Delivery to the Lungs XI, London, 2000, pp. 68–71.
16. RD Lasker. The diabetes control and complications trial, implications for policy and practice. N Engl J Med 329:1035–1036, 1993.
17. LE Mather, A Woodhouse, M Elizabeth Ward, SJ Farr, R Rubsamen, L Eltherington. Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery. Br J Clin Pharmacol 46:37–43, 1998.
18. S Mudumba, M Khossravi, D Yim, T Rossi, D Pearce, M Hughes, D Cipolla, T. Sweeney. Delivery of rhDNase by the AERx pulmonary delivery system, In: RN Dalby, PR Byron, SJ Farr J Peart, eds. Respiratory Drug Delivery VII. Buffalo Grove, IL: Interpharm Press, 2000, pp. 329–331.
19. D Cipolla, B Boyd, R Evans, S Warren, G Taylor, SJ Farr. Bolus administration of INS365: studying the feasibility of delivering high dose drugs using the AERx pulmonary delivery system. In: RN Dalby, PR Byron, SJ Farr J Peart, eds. Respiratory Drug Delivery VII. Buffalo Grove, IL: Interpharm Press, 2000, pp. 231–239.
20. D Cipolla, SJ Farr, I Gonda, R Moutvic, M Placke, T Pollock, J Schuster. Pulmonary delivery and systemic absorption of a therapeutic protein using the AERx system. J Aerosol Med 10:254, 1997.
21. F Sorgi, L Gagne, S Sharif, D Cipolla, S Farr, I Gonda, H Schrier. Aerosol Gene Delivery using the AERx delivery system. Proc Int Symp Control Rel Bioact Mater 25:184–185, 1998.
22. H Chan, E Daviskas, S Eberl, M Robinson, G Bautovich, I Young. Deposition of aqueous aerosol of technetium-99m diethylene triamine penta-acetic acid generated and delivered by a novel system, AERx, in healthy subjects. Eur J Nucl Med 26: 320–324, 1999.
23. M Robinson, D Glass, D Bailey, P Ind, A Peters. Evaluation of a new aerosol delivery device, AERx for ventilation scans in patients with chronic obstructive airways disease, COAD. Respir Crit Care Med 155:A596, 1997.
24. ME Ward, A Woodhouse, LE Mather, SJ Farr, J Okikawa, P Lloyd, J Schuster, R. Rubsamen. Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. Clin Pharmacol Ther 62:596–609, 1997.
25. M Dershwitz, J Walsh, R Morishige, P Connors, R Rubsamen, S Shafer, C Rosow. Pharmacokinetics and pharmacodynamics of inhaled versus intravenous morphine in healthy volunteers. Anesthesiology 93:619–628, 2000.
26. S Farr, A McElduff, L Mather, J Okikawa, ME Ward, I Gonda, V Licko, R Rubsamen. Pulmonary insulin administration using the AERx system: physiological and

Copyright © 2003 Marcel Dekker, Inc.

physicochemical factors influencing insulin effectiveness in healthy fasting subjects. Diabetes Tech Ther 2:185–197, 2000.
27. P Clauson, B Balent, G Briunner, G Sendlhofer, J Jendle, V Hatorp, U Dahl, J Okikawa, T Pieber. PK-PD of four different doses of pulmonary insulin delivered with the AERx diabetes management system. In: RN Dalby, PR Byron, SJ Farr J Peart, eds. Respiratory Drug Delivery VII. Buffalo Grove, IL: Interpharm Press, 2000, pp. 155–161.
28. SJ Farr, I Gonda, V Licko. Physicochemical and physiological factors influencing the effectiveness of inhaled insulin. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Buffalo Grove, IL: Interpharm Press, 1998, pp. 25–33.
29. AJ Hickey, I Gonda, W Irwin, F Fildes. Effect of hydrophobic coating on the behavior of a hygroscopic aerosol powder in an environment of controlled temperature and relative humidity. J Pharm Sci 79:1009–1014, 1990.

Copyright © 2003 Marcel Dekker, Inc.

70

Formulation Challenges of Powders for the Delivery of Small-Molecular-Weight Molecules as Aerosols

Anthony J. Hickey
University of North Carolina, Chapel Hill, North Carolina, U.S.A.

I. INTRODUCTION

Those interested in the treatment of asthma have championed the use of dry powder inhalers to deliver small-molecular-weight drug substances. The major therapeutic categories of compound delivered in this manner have been β_2-adrenergic agonists, corticosteroids, and other anti-inflammatories (mast cell stabilizers and leukotriene analogs) [1]. The general structures of the major therapeutic categories of drug are shown in Figure 1 [2]. Most of these drugs have molecular weights less than 1 kD. Macromolecular drug delivery to the lungs has been defined to include molecules >5 kDa, with a window of opportunity for transport through the lung between 5 and 20 kDa [3]. The transition from small molecular weight to large molecular weight may arbitrarily be designated to occur between 1 and 5 kD. For the purpose of this review, comments will be restricted to molecules below 1 kD and within this range biological molecules such as peptides and sugars will not be considered.

II. PATENT INFORMATION/STATUS

A number of small-molecular-weight compounds are available in the United States as dry powder products including disodium cromoglycate (Rhone-Poulenc

Copyright © 2003 Marcel Dekker, Inc.

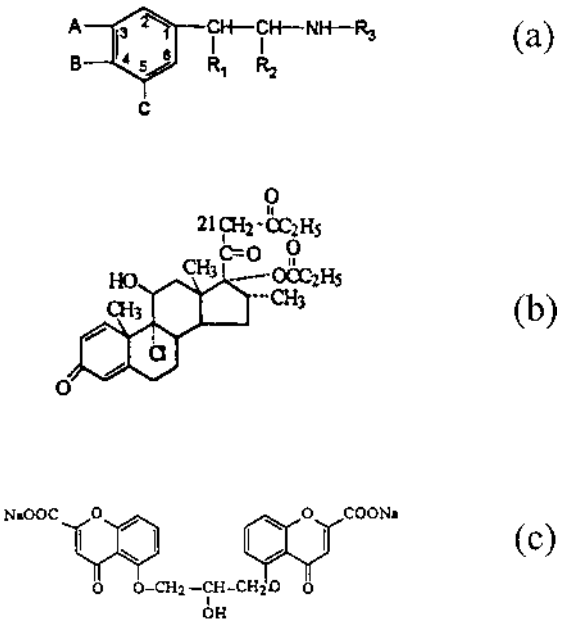


Figure 1 Chemical structures of (a) β-adrenergic agonist; (b) representative glucocorticoid (beclomethasone dipropionate); (c) disodium cromoglycate.

Rorer), albuterol, fluticosone, salmeterol, Relenza (zanamivir, GlaxoWellcome), and budesonide (Astra-Zeneca). Other compounds are available elsewhere in the world such as fenoterol (Boehringer Ingelheim) and terbutaline (Astra-Zeneca). Most of these drugs conform to the categories outlined above.

Over the last 10 years more than 60 patents on dry powder inhaler design and a smaller number on formulation strategies have been issued in the United States, Europe, and Japan (*www.patents.ibm.com*). Most of the formulation and processing patents have dealt with macromolecules. A much smaller number of patents have covered the delivery of small-molecular-weight molecules.

Patents based on physicochemical properties such as aerodynamic performance [4], surface roughness of carrier particles [5] or controlled-release properties [6] have been filed. Compositional patents on the use of salt [7], surfactants [8], complexation [9], and microcapsules [10] are also notable.

III. HISTORICAL PERSPECTIVE

Modern dry powder inhaler development was initiated in the 1960s and 1970s [11,12]. However, it could be argued that the principles of powder dispersion that

Copyright © 2003 Marcel Dekker, Inc.

launched this technology had been in existence for many years. The principles employed in devices such as the Wright's dust feed [13] and fluidized bed aerosol generator [13] can be linked closely to inhaler designs [14].

The properties of fine particles have been studied in depth. The fundamental forces of interaction [15], methods of manipulation [16], and processing steps [17] have been described in detail. The performance of dry powders has also been scrutinized. The focus of these studies has been the measurement of powder properties such as flow and dispersion [18]. Electrostatic properties have been evaluated as both static bulk [19] and aerodynamic features [20].

The key elements of dry powder inhaler systems are the formulation, the metering system, and the dispersion mechanism. Formulation approaches have historically involved precipitation or crystallization either from solution or upon spraying from a nozzle. Additional processing may have been required in the form of attrition milling to reduce the particle size to that suitable for delivery to the lungs.

Crystallization remains a major method of manufacture of particles. The two key features of crystals are their molecular, or lattice, arrangement, which can be described in terms of seven crystal systems [21,22]. These crystal systems can be divided into 32 classes based on rotational symmetry or 230 space filling categories based on Miller indices and Bravais lattices [23]. The size and shape of crystals is also dictated by the crystal habit [24]. The crystal habit is derived from the nature of particle growth. Growth, or the incorporation of molecules into the lattice system, may occur in each of the three spatial dimensions. However, growth may be inhibited in any of these directions, which will give rise to different sizes and shapes of crystal. Notably, for cubic crystals this can result in large cubes (growth in all dimensions), plates (growth in two dimensions), and rods or fibers (growth in one dimension).

Three categories of metering system may be identified. Unit (single)-dose, multiple-unit dose, and reservoir systems. Single-dose and multiple-unit dose-metering systems are somewhat inconvenient for chronic disease therapies where several doses/day are required. However, these systems offer protection for the drug from ambient environmental conditions. Reservoir systems are more convenient for long-term therapy but pose potential stability concerns due to the repeated sampling from the drug reservoir, which allows contact with the environment. Moisture ingress is the most significant potential disadvantage of such a system, which may be accompanied by microbial growth and changes in aggregation state due to capillary forces.

IV. NEED FOR THE TECHNOLOGY

There have been many stimuli to the continuous development of dry powder inhalers over the last 40 years. Initially the desire to have a handheld bolus dose

Copyright © 2003 Marcel Dekker, Inc.

delivery system that did not use propellants for commercial reasons led to powder systems. Also, a small number of patients respond poorly to propellant-driven metered-dose-inhaler delivery of aerosols. In recent years there have been two overwhelming influences for the move toward dry powder inhalers. The Montreal protocol initially limiting the use of chlorofluorocarbon propellants and ultimately banning them because of their contribution to atmospheric ozone depletion made alternatives a key to the future success of pulmonary drug delivery [25]. The need to deliver the products of biotechnology was an additional influence. Therapeutic proteins, peptides, and nucleic acids are not easily delivered by conventional routes of administration and consequently the lungs have been evaluated for this purpose.

V. DIFFERENCES FROM RELATED TECHNOLOGIES

Dry powder preparation for small-molecular-weight molecules has been limited predominantly to air-jet milling and spray drying. Over the last 5 years an increased interest in supercritical fluid manufacture of particles has arisen that may ultimately lead to an ability to control the form of the particles produced more precisely.

The most closely associated technologies to dry powder inhalers are pressurized metered-dose inhalers and nebulizers. Solution formulations delivered from pMDIs or nebulizers are immediately available for action or absorption. Suspension pMDI formulations deliver particles associated with any added excipients to the lungs. Dry powders are most closely related to these suspensions in terms of disposition from the lungs. Table 1 compares the performance of dry powders with other delivery systems from an aerosol dispersion perspective.

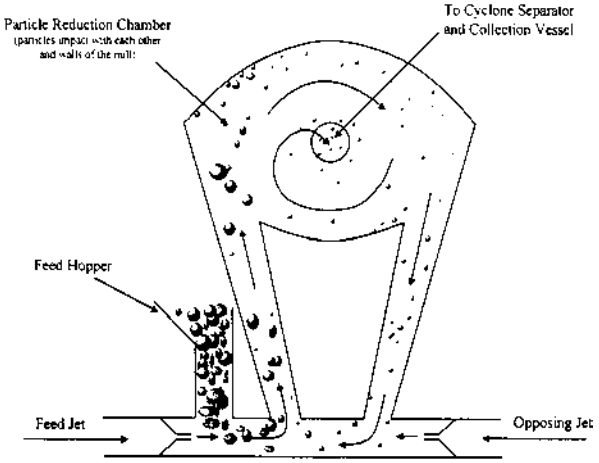
Table 1 Major Differences Between Dry Powder Aerosols and Propellant-Driven Metered-Dose Inhalers and Nebulizers

Device	Exit velocity	Particle size range (μm)	Concentration in air	Means of delivery to lungs
MDI	Fast (30 m/s at the actuator orifice)	1–10	Bolus, variable density as plume develops (dose ~ 100 μg)	Active
DPI	Variable between devices	1–10	Dense bolus (dose ~ 1–10 mg)	Active or passive
Nebulizer	Slow	0.5–5	Diffuse cloud (dose ~ 100–200 μg/min)	Passive

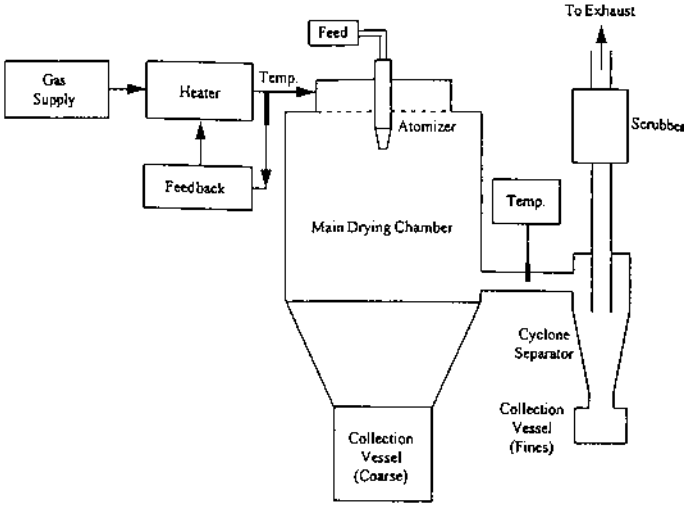
Copyright © 2003 Marcel Dekker, Inc.

VI. DESCRIPTION OF TECHNOLOGY

Air jet milling is achieved by opposing jets that bring large, unmilled particles into contact with each other fracturing them and creating smaller particles, as illustrated in Figure 2a [24,26]. Cyclone separation of particles by aerodynamic size is a feature of jet mills. A fluidizing airstream continuously mills particles


Particle Reduction Chamber
(particles impact with each other and walls of the mill)
To Cyclone Separator and Collection Vessel
Feed Hopper
Feed Jet
Opposing Jet

(a)



(b)

Figure 2 Schematic diagram of (a) air jet mill and (b) open-system spray drier.

Copyright © 2003 Marcel Dekker, Inc.

until they reach a specified size, which, depending on their density is in the range ~1–10 μm. Once this size is achieved, particles are discharged on the airstream into a collection vessel. The conveyor air is discharged through a bag filter. The conditions of mass flow rate, type of gas (usually air or nitrogen), and gas pressure (input and opposing jets) can be adjusted to optimize the process of particle production.

Spray drying involves the introduction of solution or suspension through a nozzle at high pressure into a heated container in which the solvent evaporates, as illustrated in Figure 2b [27]. The droplets dry as evaporation proceeds and are transported to a cyclone separator and air discharge similar to the jet mill described above. The conditions of solute concentration, liquid feed, drying airflow rate, and temperature can be adjusted to optimize the process of particle production.

Supercritical fluid manufacture of particles was first investigated in the nineteenth century. In the twentieth century supercritical fluid technology found a major application in chromatography. In the late 1980s and early 1990s research was being conducted to further develop technologies in this area [27,28]. In parallel, specific efforts were being made to utilize the principles in the manipulation of pharmaceutical solids [29,30] with the objective of preparing particles for inhalation [31,32].

VII. MECHANISM OF DRUG RELEASE

A. Dispersion

Small particles in the micron size range are adhesive and cohesive. The mechanisms by which the drug particles are dispersed vary. Pneumatic, vibrational, or mechanical means may be employed to disperse particles [24]. The most prominent method of dispersion is pneumatic, requiring the patient's breath to disperse the aerosol. Dispersion and delivery occurring in a single action characterize this mechanism. Active delivery devices utilizing compressed gas as a means of pneumatic dispersion do so independently of the patient's inspiratory flow and consequently separate the dispersion and delivery elements of inhaling aerosol particles.

B. Dissolution and Disposition

Dissolution occurs in the fluids within the lungs. The nature of these fluids differs depending on the region of the lung in which the aerosol deposits. Deposited particles will experience unstirred dissolution in the periphery of the lungs in the presence of thin phospholipid layers involved in maintaining the surface area for

Copyright © 2003 Marcel Dekker, Inc.

gaseous exchange. In the conducting airways particles will deposit in the stirred (by ciliary beat) thick mucus layers, which have a periciliary aqueous sublayer [33]. Depending on the dissolution rate and surface characteristics of these particles, they will experience different dissolution phenomena in these regions of the lungs. Particles that dissolve slowly will be transported on the mucociliary escalator from the lungs and therefore have a finite period of time to release drugs in the lungs before expectoration or swallowing. Particles delivered to the periphery of the lungs may be phagocytosed by macrophages and experience the low pH and enzyme replete environment of the endosome and phagolysosome [34]. The disposition of drugs from the lungs has been discussed in detail by Byron [35] and Gonda [36].

VIII. RESEARCH AND DEVELOPMENT PERTAINING TO TECHNOLOGY

A. In Vitro Studies

In vitro studies have focused on particle size determination. The majority of dry powder inhalers utilize passive dispersion of the aerosol particles. Inertial impaction is the most relevant method for the determination of particle size. The inertial, or cascade, impactor employs a defined flow rate at which it has been calibrated in terms of the aerodynamic diameter of spherical particles. This requirement renders effective evaluation of the particle size of passively dispersed dry powder aerosols difficult. A formal evaluation should be conducted over a range of selected flow rates [37,38] or over a continuously variable range of flow rates [39,40]. Inertial impactors must be recalibrated for different flow rates [41]. Continuously variable flow rates can be used, but since calibrations are meaningless under these conditions, the data obtained are useful only in relative terms.

Inability to deliver a complete or reproducible dose is the most significant effect of poor dispersion properties. Consequently, emitted doses must also be determined. The emitted dose will also depend upon the volumetric flow rate through the device for passive delivery systems. Both particle size determination and emitted dose are subject to compendial and regulatory specifications [42].

B. In Vivo Studies (Animals)

Dry powder delivery has been studied in a variety of species of animals. These studies include model compounds [43] and locally acting bronchodilators [18]. Modified particles utilizing coatings [44] and unique aerodynamic properties [45] with steroid drugs have also been evaluated in animals.

Copyright © 2003 Marcel Dekker, Inc.

C. In Vivo Studies (Humans)

Studies have been conducted to evaluate the site of deposition of dry powder in the human respiratory tract by combining drug substance with radiolabel for the performance of gamma scintigraphy [46,47].

D. In Vitro–In Vivo Correlations

Correlations were demonstrated between dissolution properties and in vivo disposition of a model compound, disodium fluorescein, delivered as a dry powder aerosol in dogs [48]. The ratio of the half-time for dissolution of coated particles to that of uncoated particles was shown to be remarkably close to similar ratios for the half-times for appearance in the plasma of dogs. On a more subtle level it was predicted [49] that manipulation of the residence time of steroids in the lungs would lead to an improved targeting of lung receptors and this subsequently proved to be the case for a coated particulate formulation [44].

IX. MAJOR OBSTACLES ENCOUNTERED DURING RESEARCH AND DEVELOPMENT AND HOW THEY WERE OVERCOME

The variability in drug delivery as a function of inspiratory flow rate for passive inhalers has been seen as a potential obstacle to broad applicability of these devices. Active dispersion systems to achieve flow rate independence have been one approach to resolving this issue. However, an interesting solution has been proposed in which the formulation itself leads to device- and flow-rate-independent in vitro performance. While this will inevitably vary from one drug to the next, some success has been achieved in this area by increasing the porosity of particles and thereby reducing the van der Waals forces of interaction [4,45]. It must be remembered, however, that the deposition in the respiratory tract itself depends on inspiratory flow rate, and therefore merely keeping the in vitro performance flow rate independent does not guarantee consistency of lung deposition and clinical safety and efficacy.

X. FABRICATION TECHNIQUES

It is often the case that particles cannot be manufactured easily without aggregating for a number of reasons. Aggregation may occur because of the fundamental forces of association such as van der Waals, capillary forces, electrostatic forces, or mechanical interlocking [50]. In addition, if particles have low melting points

Copyright © 2003 Marcel Dekker, Inc.

and high vapor pressures, they may deform on impact and aggregate to a larger extent on milling rather than being dispersed in small sizes. Furthermore, particles of this nature, even when prepared as small particles, may cohere upon storage. In certain circumstances, these phenomena and also a tendency to be heat-labile may be overcome by low-temperature milling. Any tendency to degradation by oxidation can be avoided by using inert gases rather than air as the milling fluid.

XI. SCALE-UP PROBLEMS/MANUFACTURING ISSUES

The most serious problems in scale-up for conventional dry powder inhalers are unit operations of milling, drying, blending, and filling [51]. Pilot or large-scale milling, spray drying, or blending requires process optimization not unlike any other pharmaceutical unit operation being translated from the bench scale. It is important to recognize the importance of particle size distribution, crystallinity, and polymorphism as output measures of the success of the process [52–54]. These should be matched to products from earlier stages in the research and development process.

The filling of dry powders for aerosol products poses unique challenges. Since the total fill mass for a dry powder product may be individual milligram quantities, the dose-to-dose uniformity will be influenced by handling and dispensing of the powders. Most pharmaceutical manufacturers have developed individual filling systems based on their needs. Clearly, the most difficult filling process involves capsule and blister packaging. For blends that incorporate large quantities of excipient and are filled in totals of tens of milligrams, conventional capsule-filling technology is sufficient. At individual milligram quantities different solutions are required.

Since the dispersion properties of dry powder aerosols are dependent on maintaining primary particle sizes or stable aggregates, it is important that hygroscopic products are protected from water ingress. In this regard, the packaging material itself must be considered [55]. It may be necessary to package capsules or blisters in aluminum to prevent moisture ingress altogether. For reservoir systems in which moisture will be expected to gain access, it may be necessary to utilize desiccant to reduce the local moisture content.

XII. SPECIALIZED/UNIQUE REGULATORY ISSUES

Since the number of approved excipients for use in inhaled products is small, the formulation strategies are restricted. For dry powder products the only U.S. Food and Drug Administration approved excipient is lactose. This disaccharide sugar is approved as a carrier material to help fluidize and disperse the drug and

Copyright © 2003 Marcel Dekker, Inc.

is not intended for delivery to the lungs. Consequently, to achieve controlled delivery of drugs in the lungs other materials will be required. Some obvious choices include phospholipids, specifically lecithin, other sugars, amino acids (lysine, polylysine), and nonimmunogenic proteins (HSA). The use of novel materials in lung delivery will require thorough toxicological evaluation, which in turn necessitates investment of both time and money on the part of the pharmaceutical industry.

Dissolution testing is a key issue, which has yet to be addressed fully, with regard to modified-release technology. The size and surface area of particles delivered to the lungs and the environment in which they will dissolve pose a unique problem in the evaluation of their dissolution properties. Conventional dissolution studies call for the use of large volumes of dissolution media usually contained in even larger vessels and actively mixed to achieve conditions representative of those in the gastrointestinal tract. Specific methods designed for the dissolution of particles rather than dosage forms have been adopted for aerosol products. Examples include recirculating [56] and single-pass [48] small-volume systems. However, these conditions remain distant from the physiological milieu to which aerosol products are exposed. Thus, novel systems must be evaluated and this will undoubtedly be an area of future development.

The bolus delivery of drug particles, dependent upon the breathing pattern of the patient, is not simply a volumetric flow event. Since the aerosol is dispersed on a single breath of the patient, the nature of the inspiratory flow cycle plays a role in powder dispersion and delivery. In this regard the pressure drop, rate of change of linear velocity with respect to time, which is proportional to shear in the device, and total volume of air used are major contributors to the effective delivery of aerosol particles [57].

XIII. FUTURE DEVELOPMENTS

Future developments in particle manufacture include the combination of previous techniques of manufacture with subtler drug delivery systems such as microparticles or liposomes.

Liposomes are self-assembling structures in an aqueous environment. Their long-term physical and chemical stability in this state may not be suitable for broad applications in aerosol delivery of drugs. However, they may be prepared as freeze-dried systems that can be air-jet-milled to produce particles that are stable on storage and can be used for a number of purposes [58,59]. Spray drying of liposomes for pulmonary delivery has also been attempted and may be of interest in the future [60,61].

The advantages of coating in terms of reduced dissolution rate have been demonstrated [48,56]. However, these studies used model coating materials with

Copyright © 2003 Marcel Dekker, Inc.

limited clinical potential. New coating technologies such as pulsed-laser ablation [44] may have more relevance to sustaining the residence time of drugs in the lungs. A laser beam impinges on a polymer surface thereby releasing polymer molecules, which deposit on adjacent drug particles. This technique has the advantage of giving uniform coatings with small quantities of polymer maximizing the drug content.

Nanoparticle technology may also have a role to play in drug delivery to the lungs. The ability to prepare submicron dry powder particles would result in large surface areas, which would increase intrinsic solubility and dissolution rate, making the drug more readily available for action or absorption.

REFERENCES

1. MA Kaliner, PJ Barnes, CGA Persson. Asthma: Its Pathology and Treatment. New York: Marcel Dekker, 1991.
2. A Gringauz. Introduction to Medicinal Chemistry. New York: Wiley-VCH, 1997.
3. PR Byron, JS Patton. Drug delivery via the respiratory tract. J Aerosol Med 7:49–75, 1994.
4. DA Edwards, G Caponetti, JS Hrkach, N Lotan, J Hanes, AA Ben-Jebria, RS Langer. Aerodynamically light particles for pulmonary drug delivery. US patent 5,874,064, 1999.
5. D Ganderton, NM Kassem. Aerosol carriers. US patent 5,254,330, 1991.
6. AR Baichwal, JN Staniforth. Controlled release insufflation carrier for medicaments. US patent 5,738,865, 1996.
7. AR Clark, CC Hsu, AJ Walsh. Preparation of sodium chloride aerosol formulations. US patent 5,747,002, 1998.
8. J Hanes, DA Edwards, C Evora, R Langer. Particles incorporating surfactants for pulmonary drug delivery. US patent 5,855,913, 1999.
9. DA Edwards, RS Langer, R Vanbever, J Mintzes, J Wang, D Chen. Preparation of particles for inhalation. US patent 5,985,309, 1999.
10. RN Boyes, TR Tice, RM Gilley, KL Pledger. Pharmaceutical formulations comprising microcapsules. US patent 5,384,133, 1995.
11. Intal-Cromolyn—a Monograph. Bedford, MA: Fisons Corporation, 1973, pp. 140.
12. D Ganderton, NM Kassem. Dry powder inhalers. In: D Ganderton, T Jones, eds. Advances in Pharmaceutical Sciences. London: Academic Press, 1992, pp. 165–191.
13. KH Leong. Theoretical principles and devices used to generate aerosols for research. In: AJ Hickey, ed. Pharmaceutical Inhalation Aerosol Technology. New York: Marcel Dekker, 1992, pp. 129–154.
14. RN Dalby, SL Tiano, AJ Hickey. Medical devices for the delivery of therapeutic aerosols to the lungs. In: AJ Hickey, ed. Inhalation Aerosols: Physical and Biological Basis for Therapy. New York: Marcel Dekker, 1996, pp. 441–473.
15. JN Israelachvili. Intermolecular and Surface Forces. London: Academic Press, 1992.

Copyright © 2003 Marcel Dekker, Inc.

16. W Pietsch. Size Enlargement by Agglomeration. New York: Wiley, 1991.
17. J Van Cleef. Powder technology: the powders that lend flavor, beauty and strength to many products are created by fearsome machines that force coherent materials to fail. Am Sci 79:304–315, 1991.
18. NM Concessio, MM Van Oort, M Knowles, AJ Hickey. Pharmaceutical dry powder aerosols: correlation of powder properties with dose delivery and implications for pharmacodynamic effect. Pharm Res 16:833–839, 1999.
19. JN Staniforth. The importance of electrostatic measurements in aerosol formulation and preformulation. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery IV. Buffalo Grove, IL: Interpharm Press. 1994, pp. 303–311.
20. PR Byron, J Peart, JN Staniforth. Aerosol electrostatics. I. Properties of fine powders before and after aerosolization by dry powder inhalers. Pharm Res 14:698–705, 1997.
21. JT Carstensen. Pharmaceutics of Solids and Solid Dosage Forms. New York: Wiley, 1989.
22. JT Carstensen. Pharmaceutical Principles of Solid Dosage Forms. Lancaster, PA: Technomic, 1993.
23. JW Mullin. Crystallization. 3rd ed. Oxford, UK: Butterworth-Heinemann, 1993.
24. CA Dunbar, AJ Hickey, P Holzner. Dispersion and characterization of pharmaceutical dry powder aerosols. KONA 167:44, 1998.
25. AJ Hickey, CA Dunbar. A new millenium for inhaler technology. Pharm Tech 21: 116–125, 1997.
26. AJ Hickey. Targeting of pharmaceutical aerosols to the lung: what can be learned from inhalation toxicology and industrial hygiene. Aerosol Sci Tech 18:290–304, 1993.
27. M Sacchetti, MM Van Oort. Spray-drying and supercritical fluid particle generation techniques. In: AJ Hickey, ed. Inhalation Aerosols: Physical and Biological Basis for Therapy. New York: Marcel Dekker, 1996, pp. 337–384.
28. JW Tom, PG Debendetti. Particle formation with supercritical fluids—a review. J Aerosol Sci 22:555–584, 1991.
29. A Kordikowski, P York, D Latham. Resolution of ephedrine in supercritical CO_2: a novel technique for the separation of chiral drugs. J Pharm Sci 88:786–791, 1999.
30. S Palakodaty, P York. Phase behavioral effects on particle formation processes using supercritical fluids. Pharm Res 16:976–985, 1999.
31. P York, M Hanna, BY Shekunov, GO Humphreys. Microfine particle formation by SEDS (solution enhanced dispersion by supercritical fluids): scale up by design. In RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Hilton Head, SC. Interpharm Press, Buffalo Grove, IL: 1998, pp. 169–175.
32. JC Feeley, DJ Gilbert, P Srinivas, SE Walker, P York. Engineering of particle size distributions for respiratory drug delivery by supercritical fluid processing. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Tarpon Springs, FL. Serentec, Raleigh, NC: 2000, pp. 357–360.
33. DB Yeates, GJ Besseris, LB Wong. Physicochemical properties of mucus and its propulsion. In: RG Crystal, JB West, eds. The Lung: Scientific Foundation. Philadelphia: Lippincott-Raven, 1997, pp. 487–503.
34. M Bhat, AJ Hickey. Effect of chloroquine on phagolysosomal fusion in cultured

Copyright © 2003 Marcel Dekker, Inc.

guinea pig alveolar macrophages: implications in drug delivery. AAPS PharmSci 2000. 2(4) article 34.
35. PR Byron. Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J Pharm Sci 75:433–438, 1986.
36. I Gonda. Drugs administered directly into the respiratory tract: modeling of the duration of effective drug levels. J Pharm Sci 77:340–346, 1988.
37. M Van Oort. In vitro testing of dry powder inhalers. Aerosol Sci Tech 22:364–373, 1995.
38. M Hindle, PR Byron, NC Miller. Cascade impaction methods for dry powder inhalers using the high flowrate Marple-Miller impactor. Int J Pharm 134:137–146, 1996.
39. PKP Burnell, AC Grant, PA Haywood, D Prime, BS Sumby. Powder inhalers—exploring the limits of performance. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Hilton Head, SC. Interpharm Press, Buffalo Grove, IL: 1998, pp. 259–275.
40. CA Dunbar, B Morgan, M Van Oort, AJ Hickey. A comparison of dry powder inhaler dose delivery characteristics using power performance criterion. PDA. J Pharm Sci Tech 54:478–484, 2000.
41. NC Miller. A cascade impactor for aerodynamic size measurement for MDI's and powder inhalers. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery IV. Richmond, VA. Interpharm Press, Buffalo Grove, IL: 1994, pp. 342–343.
42. PR Byron. Compendial specifications for inhaled drugs. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Hilton Head, SC. Interpharm Press, Buffalo Grove, IL: 1998, pp. 139–144.
43. RS Pillai, DB Yeates, M Eljamal, IF Miller, AJ Hickey. Generation of concentrated aerosols for inhalation studies. J Aerosol Sci 25:187–197, 1994.
44. J Talton, J Fitz-Gerald, R Singh, G Hochhaus. Nano-thin coatings for improved lung targeting of glucocorticoid dry powders: in-vitro and in-vivo characteristics. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery. VII. Tarpon Springs, FL. Serentec, Raleigh, NC: 2000, pp. 67–74.
45. J Wang, A Ben-Jebria, DA Edwards. Inhalation of estradiol for sustained systemic delivery. J Aerosol Med 12:27–36, 1999.
46. MT Vidgren, A Karkkainen, TP Paronen, P Karjalainen. Respiratory tract deposition of 99mTc-labelled drug particles administered via a dry powder inhaler. Int J Pharm 39:101–105, 1987.
47. M Vidgren, A Kärkkäinen, P Karjalainen, P Paronen, J Nuutinen. Effect of powder inhaler design on drug deposition in the respiratory tract. Int J Pharm 42:211–216, 1988.
48. RS Pillai, DB Yeates, IF Miller, AJ Hickey. Controlled dissolution from wax-coated aerosol particles in canine lungs. J Appl Physiol 84:717–725, 1998.
49. G Hochhaus, S Suarez, RJ Gonzalez-Rothi, H Schreier. Pulmonary targeting of inhaled glucocorticoids: how is it influenced by formulation. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Hilton Head, SC. Interpharm Press, Buffalo Grove, IL: 1998, pp. 45–52.
50. AJ Hickey, NM Concessio, MM Van Oort, RM Platz. Factors influencing the dispersion of dry powders as aerosols. Pharm Tech 18:58–64, 82, 1994.
51. D Ganderton, AJ Hickey. Unit processes in pharmacy: the operations. In: J Swar-

Copyright © 2003 Marcel Dekker, Inc.

brick, JC Boylan, eds. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker, 1997, pp. 1–113.
52. AJ Hickey, LD Jones. Particle-size analysis of pharmaceutical aerosol. Pharm Tech 24:48–58, 2000.
53. G Buckton. Conversions between different amorphous states and crystal polymorphs of significance for inhalation systems. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Hilton Head, SC. Interpharm Press, Buffalo Grove, IL: 1998, pp. 145–151.
54. MT Carvajal, JN Staniforth. Polymorphism and dispersibility of dry powders. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Hilton Head, SC. Interpharm Press, Buffalo Grove, IL: 1998, pp. 283–289.
55. MJ Kontny, JJ Conners, ET Graham. Moisture distribution and packaging of dry powder systems. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery IV. Richmond, VA. Interpharm Press, Buffalo Grove, IL: 1994, pp. 125–136.
56. RS Pillai, DB Yeates, IF Miller, AJ Hickey. Controlled release from condensation coated respirable aerosol particles. J Aerosol Sci 25:461–477, 1994.
57. AR Clark, AM Hollingworth. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers—implications for in vitro testing. J Aerosol Med 6:99–110, 1993.
58. H Schreier, WC Mobley, N Concessio, AJ Hickey, RW Niven. Formulation and in-vitro performance of liposome powder aerosols. STP Pharma 4:8–44, 1994.
59. WC Mobley. The effect of jet-milling on lyophilized liposomes. Pharm Res 15:149–152, 1998.
60. P Goldbach, H Brochart, A Stamm. Spray-drying of liposomes for a pulmonary administration. I. Chemical stability of phospholipids. Drug Dev Ind Pharm 19: 2611–2622, 1993.
61. P Goldbach, H Brochart, A Stamm. Spray-drying of liposomes for a pulmonary administration. II. Retention of encapsulated materials. Drug Dev Ind Pharm 19: 2623–2636, 1993.

Copyright © 2003 Marcel Dekker, Inc.

71
Nebulizer Technologies

Martin Knoch
PARI GmbH, Starnberg, Germany

Warren Finlay
University of Alberta, Edmonton, Alberta, Canada

I. INTRODUCTION

Nebulizers today fill a niche in the delivery of high doses of drug to the respiratory tract with major applications in the treatment of asthma, chronic obstructive pulmonary disease, and cystic fibrosis. A further advantage of nebulizers is their requirement of only minimal coordination and effort in comparison with pressurized metered-dose (pMDI) or dry powder inhalers (DPI). The earliest patents on nebulizers [1,2] indicate an amazingly long life cycle for nebulizer technology. Although nebulizer products are suffering from price erosion and a shrinking market share in relation to MDIs and DPIs, ongoing evolutionary innovations strengthen their position as niche products. The market is currently dominated by a huge diversity of jet nebulizers with a minor proportion of ultrasonic nebulizers. However, recent progress in manufacturing of miniaturized mechanical, electromechanical, and piezoelectric systems promises to revitalize and redefine the nebulizer market. Indeed, new piezoelectric liquid dispersion systems have the potential to form a new generation of small portable nebulizers with improved dosing capabilities, delivery efficiency, user friendliness, and safety.

In the forthcoming decade we foresee that liquid aerosol devices will split into single-breath administration for lower doses, and multiple-breath treatments over 1–3 min to administer larger drug volumes during spontaneous breathing. Table 1 lists some typical characteristics of these different aerosol delivery systems. Whereas drug release with inhalers is controlled by discrete breathing ma-

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Classification of New Liquid Inhalers and Nebulizers

Type	Administration	Treatment duration	Aerosol inhaled per breath	Aerosol inhaled per treatment	Delivery efficiency
Jet nebulizer	Consecutive spontaneous breathing	3–15 min	6–10 μL	500–2000 μL	20–40%
Electronic nebulizer	Consecutive guided breathing	1–5 min	15–20 μL	200–1500 μL	60–80%
Inhaler	Discrete single/multiple breaths	<10 breaths	20–50 μL	<500 μL	60–80%

neuvers, the new generation of nebulizers may feature an incremental release of drug aerosol during guided spontaneous breathing with integrated electronic-and-software-controlled functions. This allows improved monitoring and feedback functions that will assist the patient in receiving the most efficient treatment, enabling the clinician and practitioner to survey and optimize pulmonary treatment.

II. LIQUID DISPERSION PRINCIPLES

A. Jet Nebulizers

Jet nebulizers are driven either by a portable compressor or from a central air supply. Detailed consideration of the mechanics of jet nebulizers was given by Finlay [3]. Essentially, a high-speed airflow through a nozzle entrains and disperses the liquid into droplets (primary generation) via a viscosity-induced instability [3]. As shown in Figure 1, droplet dispersion is improved by impaction on a baffle structure (airflow controller) adjacent to the nozzle orifice transferring kinetic energy further into increased droplet surface area (secondary generation). The resulting droplet size distribution still contains only a small fraction of respirable aerosol (droplets below 5–6 μm in size) and the large droplets are recirculated within the nebulizer by means of secondary impaction structures. This process is associated with evaporation effects that cause the gas phase to be nearly saturated with water vapor, as well as a temperature decrease within the nebulizer. A considerable part of the vapor arises from the larger recirculating droplets thus increasing drug concentration in the remaining liquid. Therefore, assessment of nebulizer systems cannot be done with a simple gravimetric measurement alone [4], but also requires chemical assay.

Copyright © 2003 Marcel Dekker, Inc.

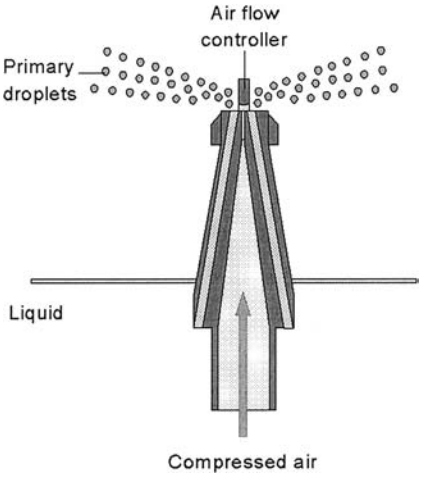


Figure 1 Droplet dispersion mechanism in a jet nebulizer.

For nebulization of suspensions, preferential containment of suspension particles in larger droplets can occur if the suspended particles are of similar size to the nebulized droplets [5], so that chemical assay may be necessary for proper particle sizing of some nebulized suspensions. For liposomal formulations, disruption of liposomes can occur due to mechanical stresses during nebulization, possibly during primary generation [6] and/or secondary generation [3], although such disruption is device-specific [7] and is most pronounced for large liposomes [8].

There are three common types of jet nebulizers: constant-output (or unvented), breath-enhanced (or vented), and breath-activated nebulizers. Constant-output nebulizers produce aerosol at a constant rate and the aerosol is diluted during inspiration by air entrainment via a T-piece or mask [9]. These nebulizers require high compressed air flows (above 6 L/min) to achieve acceptable output characteristics and treatment times. Typically at least 50% of the aerosol is wasted to the environment during exhalation. The breath-enhanced nebulizer entrains inhalation air in the droplet production region and produces aerosol at a higher rate during inspiration, but at a lower rate during expiration using a valve system. Due to this effect, approximately 70% of the aerosol will be delivered to the patient during continuous nebulization. These nebulizers may be operated by low-flow compressors (3–6 L/min) and a reduced treatment time can be achieved. Breath-actuated nebulizers release mechanically or electronically controlled doses of aerosol only during inspiration, or a portion thereof, and theoretically may improve delivery to 100% of the generated aerosol. However, beyond dose

Copyright © 2003 Marcel Dekker, Inc.

control and reduced contamination of room air, the benefits of such systems are currently relatively low owing to long treatment times and the high residual drug losses inherent with jet nebulizers.

Examples of breath-enhanced nebulizers are the Ventstream® (Medic Aid) and the Pari LC Plus® and LC Star® nebulizers (Pari Respiratory Equipment). The concept of breath-activated nebulizers has been used previously in diagnostic provocation test devices and is now entering the therapeutic arena. Examples are the Optineb® (Air Liquide), AeroEclipse® (Trudell Medical), and the HaloLite® (Medic Aid).

Hygrosopic effects, whereby droplets evaporate or grow during transit through the respiratory tract, have long been thought to be an important aspect of nebulizer behavior, but probably play only a small role in high-output-rate nebulizers owing to so-called two-way coupled effects [10]. However, hygroscopic effects play an important role in proper measurement of nebulizer particle sizes, resulting in incorrect particle sizing, particularly if the nebulized aerosol is entrained with ambient air prior to size measurement, but also if the aerosol is heated in its transit through a cascade impactor [11].

B. Ultrasonic Nebulizers

Ultrasonic nebulizers use a piezoelectric transducer to create droplets from an open liquid reservoir. Pressure waves emitted from the piezo vibrator in the bottom of the reservoir progress toward the surface forming a fountain within the wave focus. Droplets are formed by highly energetic surface instabilities in the lower part of the fountain, as shown in Figure 2 [12]. This process does not effectively aerosolize drug in suspensions, since the majority of the suspension particles are retained in the reservoir [13]. Since the energy is transferred through the liquid container it becomes evident that formulation viscosity has a strong effect on aerosol particle size and output rate, and failure may occur with high-viscosity liquids [12,14]. In most ultrasonic nebulizers the heat produced by the piezo element can result in denaturation of proteins and other thermally sensitive compounds [15]. In some devices the drug formulation is in direct contact with the piezo vibrator causing concerns regarding cleaning and microbial contamination. Newer devices avoid this problem by using decalcified or distilled water as a transfer medium in which a separate, easy-to-clean or disposable drug container is inserted. The high density of the generated aerosol makes ultrasonic nebulizers ideal for airway humidification. However, the above-mentioned constraints and high costs have limited their therapeutic use.

C. Passive Mesh-Type Piezoelectric Nebulizer

The Omron U1 nebulizer uses an ultrasonic transducer to create a longitudinal vibration of a capillary tube. This motion pumps the liquid in contact with the

Copyright © 2003 Marcel Dekker, Inc.

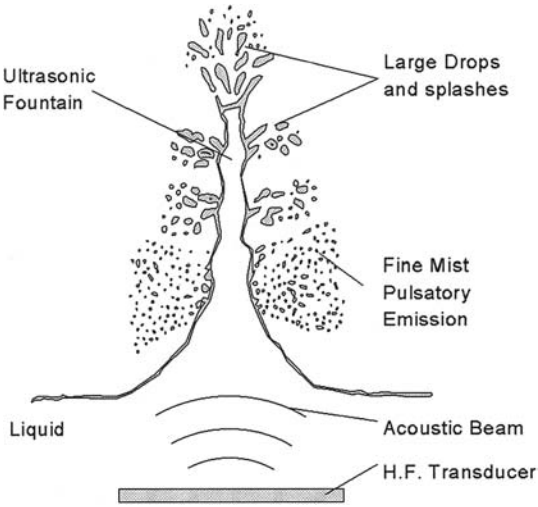


Figure 2 Droplet dispersion mechanism in an ultrasonic nebulizer. (From Ref. [12].)

lower end of the tube and ejects the liquid through a ceramic mesh adjacent to the other end. The mesh is perforated with microholes in the range of 5 μm in diameter. The advantage compared to jet and traditional ultrasonic nebulizers is the minimized residual volume in the drug reservoir. Drawbacks with respect to clogging of the holes and fragility of the ceramic mesh led to the development of the Omron U14. This system feeds controlled doses of liquid into a gap between a piezo vibrator and a mesh from which droplets are ejected. This principle is known from printer technologies. Both passive mesh-type nebulizers have a limited ability to generate sufficiently small droplets in the size range below 5 μm. The size distribution yields an MMD (mass median diameter) of approximately 7 μm and does not meet the requirements for lower respiratory tract applications.

D. Vibrating Membrane-Type Piezoelectric Systems

With this technology, a thin perforated membrane is actuated by an annular piezo element to vibrate in a resonant mode [16]. The holes have a tapered shape with larger cross section on the liquid supply side and narrower cross section on the opposite side from where the droplets emerge. The membrane vibration in conjunction with the hole shape creates pressure fluctuations and regular ejection of uniformly sized droplets. Depending on the therapeutic application, the hole sizes can be adjusted from 2 μm upward, with several hundred to several thousand holes in each membrane. Figure 3 illustrates the dispersion principle that currently is in development for a number of new aerosol delivery devices. These may

Copyright © 2003 Marcel Dekker, Inc.

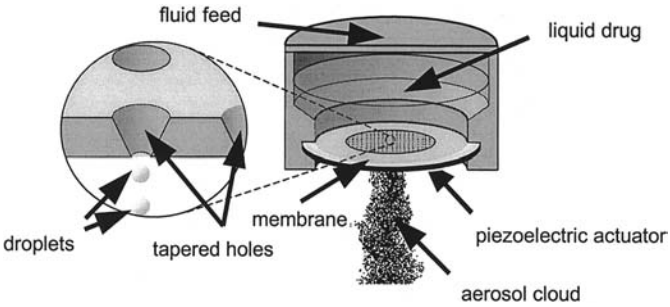


Figure 3 Droplet dispersion by a perforated vibrating membrane.

cover a wide range of requirements from low-dose single-breath applications to treatments over several minutes for the delivery of large volumes and high doses of drug solutions or suspensions. The AeroNeb® and the AeroDose® (AeroGen, Inc.) as well as the Pari Electronic Nebulizer System (e-Flow™, Pari GmbH) incorporate this technology and will enter clinical studies imminently. The impetus for the development of these systems is to improve the delivery efficiency of these devices dramatically compared to jet and traditional ultrasonic nebulizers. This should allow for much smaller liquid volumes at higher drug concentrations to be administered during each treatment, which in turn will result in shorter treatment times and better acceptability of nebulizer therapy.

E. Electrohydrodynamic Systems

Atomization by means of electrostatic charge is an old principle that has been discussed earlier for use in respiratory therapy [17]. Two electrodes are charged with a high voltage of up to 30 kV. One electrode consisting of a metal shaft contains a central capillary tube for liquid supply. On the tip of the electrode, electrostatic forces shape a liquid cone with a fine mist of droplets emerging from the tip of this cone [18,19]. Early-stage prototypes based on this principle have demonstrated feasibility to generate aerosols suitable for inhalation [20]. However, this principle requires drug formulations with distinct physical properties. In particular, liquids with certain conductivities and low surface tension, such as ethanol, are preferred [17].

III. REGULATORY ISSUES

In the past, a wide variety of nebulizers were accepted by regulatory bodies for use in clinical trials. Only rarely were specific requirements defined for nebulizer

Copyright © 2003 Marcel Dekker, Inc.

characteristics, and in many cases a distinct system was chosen as representative of nebulizer treatment as a whole. While pMDIs and multidose DPIs require approval as a drug product, refillable nebulizers were regarded as mechanical devices and are approved in the United States via a simple 510k submission procedure. This generic approach to nebulizers contributed to poor regulation and affected the reputation of nebulized aerosol therapy owing to quality deficiencies of some nebulizer products (indeed, for a given drug the dose reaching the lungs may vary by a factor of 10 among different nebulizer brands). Recognition of drug and nebulizer interactions and severe interdevice differences in lung deposition resulted in the specific selection of nebulizers for regulatory approval of new drug formulations. Examples are the Food and Drug Administration (FDA) approval of Pulmozyme® (Genentech, Inc.) for use with three distinct nebulizers in the United States and its worldwide registration for a number of nebulizers selected according to a standardized test protocol. Further examples are the FDA approval and registration in Europe of Tobi® (PathoGenesis) and the FDA approval of Pulmicort® suspension (AstraZeneca) both with the LC Plus® nebulizer (Pari Respiratory Equipment) being selected for the final phase III clinical trials. Better-controlled clinical trials and tightened product specifications now build a link between drug and device with improved safety and efficacy in nebulizer therapy. However, use of a drug with devices other than those approved or registered cannot completely be prevented. In the future, new devices will be developed and customized to meet specific requirements of the drug and its target use. The new proprietary delivery technologies and device-specific liquid container systems will result in a combined regulatory approval of drug and nebulizer device to optimize safety and efficacy of inhaled drug therapy.

REFERENCES

1. P Giffard. Improvement in vaporizers. US patent 211,234, 1878.
2. AJ Palmer, GH Palmer. Kaiserliches patentamt. Zerstaeuber patent 47181, 1888.
3. WH Finlay. An Introduction to the Mechanics of Inhaled Pharmaceutical Aerosols. London: Academic Press, 2001.
4. JH Dennis, SC Stenton, JR Beach, AJ Avery, EH Walters, DJ Hendrick. Jet and ultrasonic nebuliser output: use of a new method for direct measurement of aerosol output. Thorax 45:728–732, 1990.
5. WH Finlay, KW Stapleton, P Zuberbuhler. Predicting lung dosages of a nebulized suspension: Pulmicort (Budesonide). Particulate Sci Tech 15:243–251, 1997.
6. KMG Taylor, SJ Farr. Preparation of liposomes for pulmonary drug delivery. In: G Gregoriadis, ed. Liposome Preparations and Related Techniques. 2nd ed. Vol. 1. Boca Raton, FL: CRC Press, 1993, pp. 177–195.
7. WH Finlay, JP Wong. Regional lung deposition of nebulized liposome-encapsulated ciprofloxacin. Int J Pharm 167:121–127, 1998.

Copyright © 2003 Marcel Dekker, Inc.

8. RW Niven, M Speer, H Schreier. Nebulization of liposomes II. The effects of size and modelling of solute release profiles. Pharm Res 8:217–221, 1991.
9. M Knoch, E Sommer. Jet nebulizer design and function. Eur Respir Rev 10:183–186, 2000.
10. WH Finlay. Estimating the type of hygroscopic behaviour exhibited by aqueous droplets. J Aerosol Med 11:221–229, 1998.
11. WH Finlay, KW Stapleton. Undersizing of droplets from a vented nebulizer caused by aerosol heating during transit through an Anderson impactor. J Aerosol Sci 30: 105–109, 1999.
12. RMG Boucher, J Kreuter. The fundamentals of the ultrasonic atomization of medicated solutions. Ann Allergy 26:591–600, 1968.
13. K Nikander, M Turpeinen, P Wollmer. The conventional ultrasonic nebulizer proved inefficient in nebulizing a suspension. J Aerosol Med 12:47–53, 1999.
14. WH Finlay, CF Lange, M King, D Speert. Lung delivery of aerosolized dextran. Am J Respir Crit Care Med 161:91–97, 2000.
15. DC Cipolla, AR Clark, H-K Chan, I Gonda, SJ Shire. Assessment of aerosol delivery systems for recombinant human deoxyribonuclease. STP Pharma Sci 4:50–62, 1994.
16. N Maehara, S Uhea, E Mori. Influence of the vibrating system of a multipinhole-plate ultrasonic nebulizer on its performance. Rev Sci Instrum 57:2870–2876, 1986.
17. BJ Greenspan. Ultrasonic and electrohydrodynamic methods for aerosol generation. In: AJ Hickey, ed. Inhalation Aerosols. New York: Marcel Dekker, 1996, pp. 313–335.
18. GMH Meesters, PHW Vercoulen, JCM Marijnissen, B Scarlett. Generation of micron-sized droplets from the Taylor cone. J Aerosol Sci 23:37–49, 1992.
19. A Jaworek, A Krupa. Generation and characteristics of the precession mode of EHD spraying. J Aerosol Sci 27:75–82, 1996.
20. WC Zimlich, JY Ding, DR Busick, RR Moutvic, ME Placke, PH Hirst, GR Pitcairn, S Malik, SP Newman, F Macintyre, PR Miller, MT Shepherd, TM Lukas. The development of a novel electrohydrodynamic pulmonary drug delivery device. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 241–246.

Copyright © 2003 Marcel Dekker, Inc.

72

The Pressurized Metered-Dose Inhaler

Akwete L. Adjei
Kos Pharmaceuticals, Inc., Edison, New Jersey, U.S.A.

I. INTRODUCTION

Inhalation aerosols may be defined as colloidal systems containing finely subdivided liquid or solid particles dispersed in a gas. The dispersed phase must satisfy certain size limits, usually <50 μm but preferably <10 μm [1]. Importantly, the medicinal pressurized aerosol product must qualify as a surface-active drug system for rendering therapy that is self-contained and sprayable wherein the continuous phase is a liquefied gas [2]. A historical summary of the evolution of this technology is given in Table 1.

The pressurized metered-dose inhaler (pMDI) is largely used in ameliorating diseases of the airways. Having originated from the perfumery industry and the environmental sciences in the late nineteenth century, this technology initially used dynamic energy as a means of aerosolizing a binary spray solution of methylene and ethylene chloride [3]. Not long after this, carbon dioxide replaced the alkyl halides as propellant, thus enabling the creation of a portable, glass dispenser [4] aerosolizer for perfumes. The breakthrough into the pharmaceutical arena occurred in 1921 when solutions of antiseptics were successfully aerosolized [5] using portable, nozzle-configured, glass or metal containers. Dimethylethane, isobutane, methylene chloride, and vinyl chloride were employed as propellants [6,7]. Over the last 60 years hydrofluoroalkanes (HFC) [8] and chlorofluorcarbons (CFC) have been successfully introduced as pharmaceutically safe propellants. These are available commercially worldwide as insecticides [9–11] and medicines for remedial health [12]. A typical anatomy of the pMDI is

Copyright © 2003 Marcel Dekker, Inc.

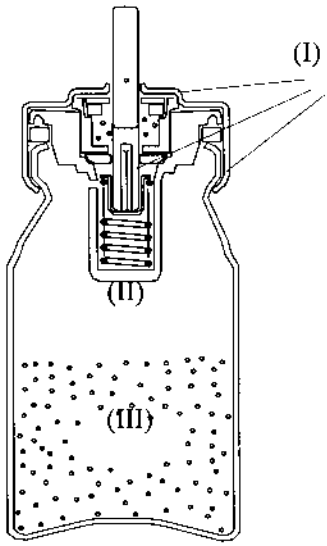
Table 1 Historical Summary of Inhalation Drug Delivery

Date	Event
3000 B.C.	Chinese used Ma Huang, a forerunner of ephedrine
2000 B.C.	Indus Valley: inhaled smokes/fumes (breathlessness) Hippocrates: inhalation (medicate lung and upper airways)
1135–1204	Maimonides, "Treatise on Asthma": organization of disease treatment
1802	Fumes of pulverized datura roots as a means of treating pulmonary hyperresponsiveness (imported from India to England)
1866	Herman Beigel, "On Inhalation as a Means of Local Treatment of Organs of Respiration by Atomized Fluids and Gases"
1940s	Development of pressurized-pack aerosols
1942	Goodhue and Sullivan, USDA, develop insecticide, US patent 2,321,023
1950s	Topical aerosols (burns, cuts, bruises, infections, rash); MDI of epinephrine, first aerosol for local delivery to lung
1980s	Dry powder inhalation aerosols introduced as a means for treating lung disease

given in Figure 1, which, as shown, is a reservoir system in which the formulation is in equilibrium with a gaseous headspace comprising propellant, moisture, and any other volatile substance present in the product. The seals in the primary closure system are usually fabricated with elastomeric, plastic, and stainless steel components. Therefore, it is conceivable that gas exchange across the nozzle would be spontaneous over time, and that this would have a measurable impact on suspension quality such as Oswald ripening, stability, and uniformity of dosage units during normal storage.

The idea to deliver drugs locally to the pulmonary system for remedial health has been known over the centuries. In 3000 B.C., Chinese health care artisans used smokes of Ma Huang, a forerunner of ephedrine, to treat breathing anomalies. However, it was not until 2000 B.C. before Indus Valley caregivers, also Hippocrates, were able to systematically begin to use medication of the lung and upper airways as a means to treat asthma. From about 1135 to 1204, Maimonides organized fundamental data on the subject that served as a basis for his "Treatise on Asthma," the very first time a systematic method for treating this and other lung diseases was presented. This inspired exportation of pulverized datura roots by Indian traders in the late 1700s to early 1800s, which the English used extensively for treating organs of respiration, enunciating protocols still in use today for pulmonary clinical therapeutics. In 1942, a U.S. government–sponsored project produced the first insecticide product [11], which later yielded a number of topical aerosols for treating burns, cuts, bruises, infections, and rash. The first inhalation pMDI patent was issued to Riker Laboratories [13]. Several

Copyright © 2003 Marcel Dekker, Inc.



I. Sealing mechanism of metered valve
II. Vapor phase in the MDI - propellant vapor
III. Condensed phase - drug, surfactant, solvent and propellant

Figure 1 Anatomy of the pressurized metered-dose inhaler.

drugs were claimed in this patent. These include prednisolone, epinephrine, isoproterenol, phenylephrine, phenyl propanolamine, methapyrilene, and their salts as well as their mixtures; hydrocortisone and neomycine, their salts, alone or in combination with each other as well as β-agonists; cyanocobalamine; glucagon and insulin; chlorotetracycline and its salts; and, finally, adrenochrome (ACTH) and its analogs. Since that time, pMDIs have been used to administer corticosteroids, mucolytics, anticholinergics, and bronchodilators to the lower reaches of the lung to treat local as well as systemic disease. The commercially available products are unquestionably the most effective mode for treating patients with asthma, chronic obstructive pulmonary disease (COPD), and a number of other allergic airway diseases. The pMDI appears also adaptable to biotherapeutic drugs because, unlike when administered orally, these compounds when properly formulated can maintain their primary and secondary structure without much change to bioactivity and conformational integrity [14]. For the most part, these products are formulated to provide injection-like kinetics, but of late, a number of investigations are concentrating on modified-release technology platforms, which is the focus of this chapter.

Copyright © 2003 Marcel Dekker, Inc.

II. MODULATED-RELEASE SYSTEMS

Dose frequency and rapid absorption of drugs via the lung, and therefore short durations of biological activity, may be a key reason for developing modulated systems for the pMDI. Short lung residence time of small molecules (i.e., high clearance rates) and low degree of absorption of macromolecular drugs are characteristic of drugs delivered to the lung. Besides changing the molecular nature of the molecule by derivatization by covalent bonding, ion pairing, or other chemical means to form slow-dissolving, lipophilic, and surface energetically hindered species, there may be two physical approaches to achieving modulation in inhaled aerosol science. These include: (a) altering the microenvironment of the drug particles in the respiratory tract, thus improving lung retention, and (b) creating aerosolized drug particles with micromeritic quality that capitalizes on alveolar deposition and lymphatic uptake, and puts the drug substance below areas cleared by the mucociliary escalator. The object of each method is primarily to optimize the pharmacodynamics of the dosage form while simultaneously limiting the concentration—dependent side effects of the active pharmaceutical ingredient.

A. Micromeritics

It is generally known that particles deposit in the airways based upon their aerodynamic diameter. At low particle velocities, particles greater than 5 μm generally deposit in the oropharynx and central and transitional airways while particles smaller than 5 μm predominantly deposit in the alveolar and respiratory regions of the lung [15–17]. Pulmonary drug absorption is dependent on drug dissolution, diffusivity, permeability, and lymphatic flow, as well as on the elimination pathways competing with absorption into the blood compartment. Phagocytosis by alveolar macrophages is important for particulates. Metabolism may occur. The most universal mechanism of elimination is mucociliary clearance from the conducting airways. It would therefore be expected that deposition in the deep lung, beyond the reach of the mucociliary escalator, would enhance the residence time, and hence the extent of absorption, of drugs deposited in the lung.

The work of Newman et al. [18] suggests, indeed, that increase of residence time and pulmonary absorption following deposition of a fine-particle aerosol are improved markedly over results for a coarse aerosol of the same drug. Similar observations have been made by other investigators [19] where fractional bioavailability of a number of biotherapeutic drugs demonstrated significant increases compared to coarse, instilled formulations (Table 2). Figures 2 and 3 summarize the improvements that a suspension pMDI presentation of leuprolide acetate formulated to a fixed range of particle size distribution would make to LH-RH therapy compared to a depot formulation of this drug. These plots suggest blood levels of the endogenous hormone LH-RH, obtained with the pMDI, would

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Deposition and Retention of Aerosolized Peptides: Effect of Regional Deposition in New Zealand Rabbits

	IT		Aerosol	
	$K_{le}(hr^{-1})$	F	$K_{le}(h^{-1})$	F
Oxytocin	2.34 ± 0.29	8.7	0.918 ± 0.088	67.7
Insulin	0.846 ± 0.141	5.6	0.440 ± 0.14	57.2
hGH	0.062 ± 0.012	15.5	0.078 ± 0.039	44.8
$K_{mce}(h^{-1})$	1.12 ± 0.28		0.554 ± 0.11	

IT, intratracheal administration; K_{le}, rate constant for all elimination processes from the lung except absorption into the blood compartment; F, relative bioavailability in %; hGH, human growth hormone; K_{mcc}, rate constant for mucociliary clearance.

yield optimal gonadotropin concentrations that slow production of endometrial lesions without engendering significant bone loss in endometriosis patients compared to the injectable product.

B. Liposomal Systems

Liposomes are lipid bilayers often used to encapsulate water-soluble as well as water-insoluble compounds. Particle size, drug loading, charge on the dispersed

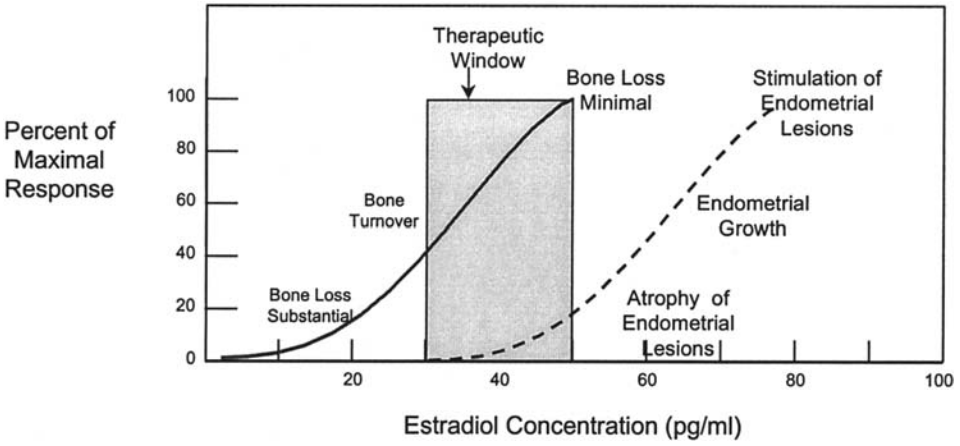


Figure 2 Improvements to endometrial therapy with inhaled LH-RH therapy; estradiol levels in endometrial female patients.

Copyright © 2003 Marcel Dekker, Inc.

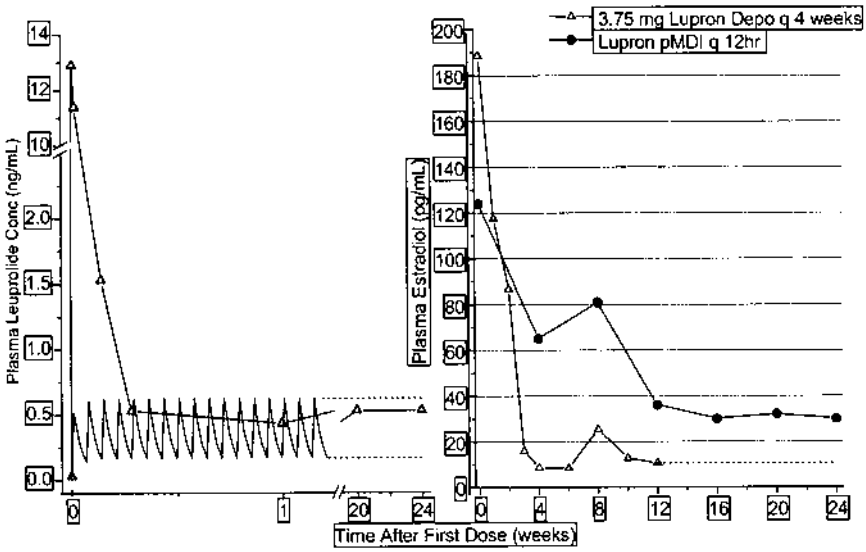

3.75 mg Lupron Depo q 4 weeks
Lupron pMDI q 12hr
Plasma Leuprolide Conc (ng/mL)
Plasma Estradiol (pg/mL)
Time After First Dose (weeks)

Figure 3 Improvements to LH-RH therapy by formulation presentation as a pressurized metered-dose inhaler compared to lupron depo.

phase, and site of deposition in the airways contribute to the rate of uptake and overall lung residence time of the drug. Coating surfaces of liposomes has been shown to result in significant carrier redistribution to the lung [20,21]. A significant amount of data is also available that demonstrates improved safety and efficacy of a number of inhalation drug delivery systems [22]. Inhaled liposomal products easily break down within the airways, especially the alveoli. The resulting lipid constituents enter the pulmonary surfactant pool for absorption and distribution to the systemic circulation [23]. But it is the physical structure of liposomes wherein the medicament is encapsulated in lipid bilayers that importantly promotes prolonged drug release in the airways (Table 3). Further, by perturbing the structure of the liposomal vesicles, one is able to tailor a particular mode of release as well as extent of drug action in the lung. This alteration in drug distribution to the vasculature is primarily what appears to result in modulation of effect of the drug, i.e., increased residence time and a consequent decrease in absorption half-life.

C. Polymer Matrices and Encapsulated Systems

Microspheres and other microparticle delivery systems use slow-dissolving polymeric systems to modulate the rate of release in the airways just like they do with

Copyright © 2003 Marcel Dekker, Inc.

Table 3 Mean Pharmacokinetic Parameters Following the Inhalation of 20 mg Free or Liposomal Sodium Cromoglycate in Five Healthy Volunteers

	Mean ± SD (n = 5)	
Parameter (units)	Free drug	Liposomal drug
C_{max} (ng/mL)	34.88 ± 7.76	4.69 ± 1.37
T_{max} (min)	21.0 ± 4.0	30.0 ± 4.1
Area under curve to infinity (μg*h/L)	101.71 ± 27.04	101.97 ± 24.08
Mean residence time (h)	2.65 ± 0.22	92.53 ± 24.27

Source: Adapted in part from Refs. [32, 33].

intramuscular or implantable drug delivery systems [24–28]. When aerosolized to the lung, the rate of dissolution of the polymer determines the magnitude of local as well as systemic drug concentrations to the extent that the end effect of dissolution, permeability, and uptake of the drug determines the degree of the drug's action in the body. This provides for a means to control pharmacological response of the drug product. The encapsulated drug may also distribute to nonpulmonary sites via alveolar macrophages, which also modulate the pharmacodynamics of the drug product as lymphatic uptake becomes a rate-limiting step. Modulation of a prototype hormone drug using the pMDI with a semisynthetic, biocompatible polymer is shown for New Zealand rabbits in Figure 4. Comparative performance against an intravenous control formulation (half-life = 5 min) shows bioavailability of the aerosol to be about 50% with durations of action for the pMDI extending possibly to beyond 4 h.

D. Salt Forms, Ion Pairing, and Coprecipitates

Salts have been widely used to modulate product characteristics such as dissolution and absorption because often solutions of salts are absorbed at faster rates than suspensions of the nonsalt forms [29]. Generally, coprecipitation produces particles with drastically reduced rates of dissolution in non-aqueous media, which, like salts and ionic species, are insoluble in propellant systems, thus impacting on the extent of drug release in the lung [30].

E. Prodrugs and Pegylation

Prodrugs are chemically modified drug substances while pegylated molecules are noncovalently linked complexes with polyethylene glycol. Both of these molecular species transform into their respective parent forms once in the lung, the chemical transformation process being absorption rate limiting. The impact of

Copyright © 2003 Marcel Dekker, Inc.

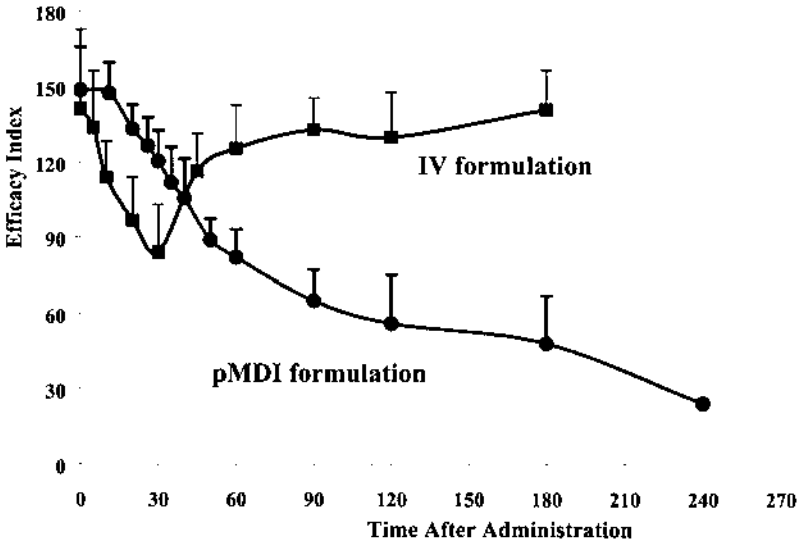


Figure 4 Biological effect of a model protein in New Zealand Rabbits using polymer matrixed aerosol particles ($n = 6$).

pegylation on modulation of release and effect of rhG-CSF in laboratory animals from a dry powder inhalation aerosol has been elegantly presented by Niven [31]. These findings should be applicable for pMDI formulations as well, although conclusive literature data on the subject are not available at this time.

III. CONCLUSIONS

This chapter has attempted to evaluate the scope of modulated-release aerosol formulations in drug research as regards application of pMDI technology. A number of formulations and excipients have been reported in the literature that teach various methods for controlling and regulating the release of inhaled drug aerosol particles in the lung milieu. Formulation concepts, pulmonary delivery technologies, drug substance chemistry, and pulmonary pathophysiology are crucial issues that could have an impact on clinical utility of modulated-release drug systems administered to the airways for chronic use in palliative care. Data available to date nonetheless indicate that the development of these aerosol drug products is feasible. The formulation concepts summarized here may provide added impetus to the promise shown thus far by the lung to be a feasible port of drug entry to the body, especially in the area of modulation of peptides, proteins, oligonucleo-

Copyright © 2003 Marcel Dekker, Inc.

tides, and other macromolecular drugs. However, until sufficient safety data are available for these formulation concepts, optimism surrounding their clinical usefulness must be tempered.

REFERENCES

1. D Sinclair. Handbook on Aerosols. Washington, DC: 1950, pp. 64.
2. CSMA. Aerosol Guide. 1957, pp. 27.
3. H Helbing, G Pertsch. Collodium mixture. US patent 628,463, 1889.
4. RW Moore. Perfumery atomizer. US patent 746,866, 1903.
5. LK Mobley. Method of applying liquid antiseptics. US patent 1,378,481, 1921.
6. E Rotheim. Method and apparatus for atomizing materials. US patent 1,892,750, 1931.
7. E Rotheim. Method and apparatus for atomizing or distribution of liquid or semisolid materials. US patent 1,800,156, 1931.
8. TM Midgley, Jr. AL Henne, RR McNary. Process of preventing fire by nontoxic substances. US patent 1,926,396, 1933.
9. LD Goodhue. Insecticidal aerosol production: spray solutions and liquified gases. Ind Eng Chem News 34:1436, 1942.
10. LD Goodhue, WN Sullivan. Method of applying parasiticides. US patent 2,321,023, 1943.
11. WN Sullivan, LD Goodhue, JH Fales. Toxicity to adult mosquitoes of aerosols produced by spraying solutions of insecticides in liquefied gas. J Econ Ent 35:48, 1942.
12. JW Soffer. Beaded-stem dispensing valve for gas-pressure containers. US patent 2,788,924, 1953.
13. CG Thiel. Self-propelling powder dispensing compositions. US patent 3,014,844, 1961.
14. A Adjei, J Garren. Pulmonary delivery of peptide drugs: effect of particle size on bioavailability of leuprolide acetate in healthy male volunteers. Pharm Res 7:565–569, 1990.
15. ER Weibel. Morphometry of the Human Lung. Berlin: Springer-Verlag, 1963, pp. 1–151.
16. KH Kilburn. Functional morphology of the distal lung. Int Rev Cytol 37:153–270, 1974.
17. JB Forrest. Lower airway: structure and function. In: MF Newhouse, MB Dolovich, eds. Aerosols in Medicine, Principles, Diagnostics and Therapy. New York: Elsevier, 1985, Chapter 2.
18. S Newman, PH Hirst, GR Pitcarin, AR Clark. Understanding regional lung deposition data in gamma scintigraphy. respiratory drug delivery. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Buffalo Grove, IL: Interpharm Press, 1998.
19. P Colthorpe, S Farr, G Taylor, I Smith, ID Wyatt. The pharmacokinetics of pulmonary-delivered insulin: a comparison of intratracheal and aerosol administration to the rabbit. Pharm Res 9:764–768, 1992.

Copyright © 2003 Marcel Dekker, Inc.

20. M Takada, T Yuzuriha, K Katayama, K Iwamoto, J Sunamoto. Increased lung uptake of liposomes coated with polysaccharides. Biochim Biophys Acta 802:237–244, 1984.
21. T Sato, K Sakai, K Akiyoshi, J Sunamoto. Cell recognition of liposome as coated with cell specific polysaccharides. Proc Int Symp Control Rel Bioact Mater 15:231–232, 1988.
22. P Gupta, A Adjei. Pulmonary Delivery of Therapeutic Peptides and Proteins. New York: Marcel Dekker, 1997, Chapter 26, Table 4, pp. 798–801.
23. A Pettanazzo, A Jobe, M Ikegami, R Abra, P Mihalko. Clearance of phosphatidylcholine and cholesterol from liposomes, liposomes loaded with metaproterenol, and rabbit surfactant from adult rabbit lung. Am Rev Respir Dis 139:752–758, 1989.
24. TR Tice, DR Cowsar. Biodegradable controlled-release parenteral systems. Pharm Technol 8:26–35, 1984.
25. Y Ogawa, M Yamamoto, H Okada, T Yashiki, T Shimamoto. A new technique to efficiently entrap leuprolide acetate into microcapsules of polylactic acid or copoly lactic/glycolic acid. Chem Pharm Bull 36:1095–1103, 1988.
26. FG Hutchinson, BJA Furr. Biodegradable polymers for controlled release of peptides and proteins. In: FHD Roerdink, AM Kroon, eds. Drug Carrier Systems. New York: John Wiley & Sons, 1989, pp. 111–153
27. PK Gupta. Drug targeting in cancer chemotherapy: a clinical perspective. J Pharm Sci 79:949–962, 1990.
28. T Kissel, Z Brich, S Bantle, I Lancranjan, N Nimmerfall, P Vit. Parenteral depot-systems on the basis of biodegradable polyesters. J Control Rel 16:27–42, 1991.
29. ZT Chowhan, AA Amaro. Pulmonary absorption studies utilising in situ rat lung model: designing dosage regimen for bronchial delivery of new drug entities. J Pharm Sci 65:1669–1672, 1976.
30. R Niven, P Byron. Solute absorption from the airways of the isolated rat lung. I. The use of absorption data to quantify drug dissolution or release in the respiratory tract. Pharm Res 5:574–579, 1988.
31. R Niven, Feasibility studies with recombinant human granulocyte colony stimulating factor. In: A Adjei, P Gupta, eds. Inhalation Delivery of Therapeutic Peptides and Proteins. Lung Physiology Series. New York: Marcel Dekker, 1997, Chapter 15, pp. 419.
32. KMG Taylor, G Taylor, IW Kellaway, J Stevens. The influence of liposomal encapsulation on sodium cromoglycate pharmacokinetics in man. Pharm Res 6:633–636, 1989.
33. IW Kellaway, KMG Taylor, G Taylor, J Stevens. The pharmacokinetics of liposomal sodium cromoglycate nebulised to volunteers. Proc Int Symp Control Rel Bioact Mater 15:197–198, 1988.

Copyright © 2003 Marcel Dekker, Inc.

73

Passive Dry Powder Inhalation Technology

Ian Ashurst and Ann Malton
GlaxoSmithKline R&D, Ware, Hertfordshire, England

I. INTRODUCTION

The Montreal Protocol in 1989, implementing the phaseout of the use of chlorofluorocarbon propellants, renewed the impetus for introducing passive dry powder inhalers (DPIs) for respiratory disease treatment as an alternative to pressurized metered-dose inhalers (pMDIs). Although alternative propellants have been found, they are still environmentally sensitive, and the pMDIs have an added disadvantage of requiring patient coordination of dose delivery with inhalation, something many patients cannot successfully achieve. Passive dry powder inhalers deliver the dose of drug in a powder cloud when the patient inhales through the device; they are easy to operate and user friendly. Table 1 summarizes the advantages and disadvantages of DPIs in comparison with pMDIs.

More than 10 years later, the global inhalation drugs market has mushroomed, with an increase in the diagnosis and treatment of respiratory diseases. The size of the inhaled antiasthma drug market is currently $9 billion. Interestingly, there are significant trends in favored therapy in different countries; for example, Scandinavia favors DPIs, whereas the U.S. market still prefers pMDIs using propellants. Worldwide, the two landmark, passive DPIs are regarded as the Diskus™/Accuhaler™ inhaler (GlaxoSmithKline) and the Turbuhaler™ inhaler (AstraZeneca). This chapter compares the characteristics of these two devices as being typical of the passive DPI technology.

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Typical Advantages and Disadvantages of DPIs, Compared with Pressurized pMDIs

Advantages
Propellant free
Less need for patient coordination
Less potential for formulation problems
Less potential for extractables from device components
Disadvantages
Dependency on patient's inspiratory flow rate and profile
Device resistance/design issues
Greater potential problems in dose uniformity
Less protection from environmental effects/patient abuse
More expensive than pMDIs
Not available worldwide

Source: Reprinted from Ref. [10] with permission from Elsevier Science.

II. HISTORICAL DEVELOPMENT

Since the introduction of the first single-dose DPI, the Spinhaler™ [1], 30 years ago, further devices were developed that were easier to manipulate, such as the Rotahaler™ [2], and which incorporated four and eight doses, such as the Diskhaler™ [3].

In 1988 the first multiple-dose device, the Turbuhaler inhaler, appeared on the market [4]. A reservoir containing up to 200 doses of drug powder blend is incorporated in the inhaler. The patient dispenses a dose at the point of inhalation by twisting the base of the device. The Turbuhaler quickly established its prominence in the inhalation product market, as the first real alternative to the convenience and effectiveness of a pMDI.

In the mid-1990s, the Diskus/Accuhaler inhaler [5] was launched with an alternative design principle of factory-metered doses contained in a blister strip. This arrangement combines the convenience of a month's therapy with the advantage of an improved precision of powder dispensing and environmental protection of the individual doses.

The advantages and disadvantages of factory-metered or reservoir designs have been debated ever since [6]. Factory-metered dose designs are more expensive to manufacture, but produce a high-quality, consistent dosing performance. Reservoir designs are cheaper to manufacture, but may deliver variable doses [7]. Consequently, newer alternatives to the Diskus and Turbuhaler inhalers may be required to demonstrate significant advantages to establish their own place in a competitive market.

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Currently Marketed DPIs

Single-dose factory-metered	Multidose factory-metered	Multidose patient-metered
Spinhaler™ (Fisons/Aventis)	Diskhaler™ (GlaxoSmithKline)	Turbuhaler™ (AstraZeneca)
Rotahaler™ (GlaxoSmithKline)	Diskus/Accuhaler™ (GlaxoSmithKline)	Pulvinal™ (Chiesi)
Inhalator™ (Boehringer-Ingelheim)		Easyhaler™ (Orion)
Cyclohaler™ (Pharmachemie)		Clickhaler™ (ML Laboratories)
Flowcaps™ (Hovione)		Ultrahaler™ (Rhone-Poulenc Rorer/Aventis)

Source: Reprinted with modifications From ref. [10] with permission from Elsevier Science.

III. CURRENTLY MARKETED PASSIVE DRY POWDER INHALERS

Table 2 lists a number of currently marketed DPIs in categories of single or multidose breath-actuated (or "passive") DPIs. The breath actuation in the devices refers to the aerosolization of the dry powder by the patient's breathing. Some of the first effective drugs for asthma, such as salbutamol, have now reached the end of their patent life, and have thus prompted an explosion of new inhalation devices marketed with the original drug, with claimed advantages such as reduced cost. At the same time, the original designs of passive DPIs, which contained only single or few doses, have been superseded by new designs of inhaler containing a

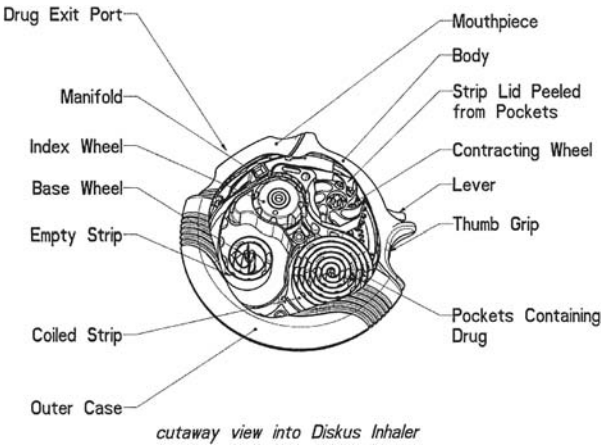


Figure 1 Cutaway view of the Diskus Inhaler. (Courtesy of GlaxoSmithKline.)

Copyright © 2003 Marcel Dekker, Inc.

month's therapy in multiple premetered-dose packs or "reservoir" designs containing bulk drug for dispensing into individual doses by the patient. The current market for DPIs has approximately 20 devices in present use and at least another 30 under development. Clinicians recognize that DPIs are a suitable alterative to pMDIs for some patients, but the relative performance of alternative devices is often unclear.

A. The Diskus Inhaler

Figure 1 is a schematic of the Diskus device. The design is a development of the approach used in the Diskhaler device where the dose is encapsulated in a blister, which is sealed with foil to protect the powder from the environment

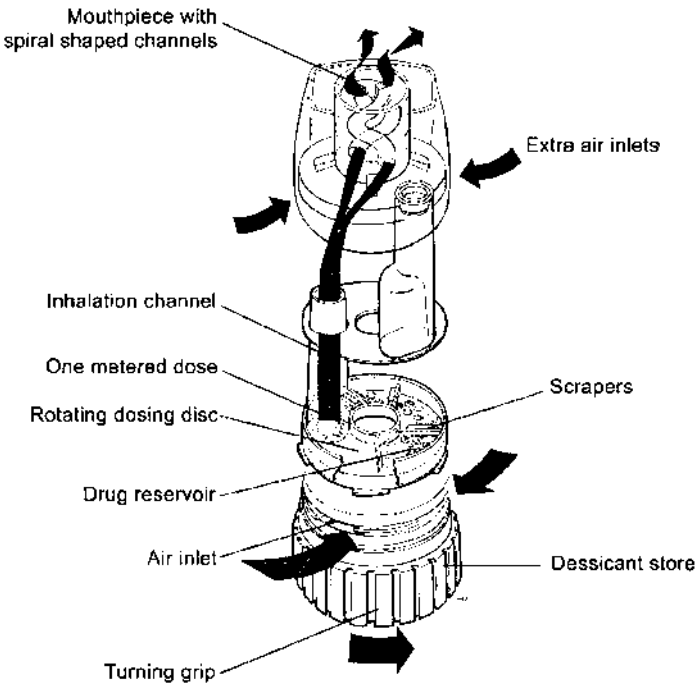


Figure 2 The Turbuhaler inhaler (AstraZeneca) is an inspiratory flow-driven, multidose dry powder inhaler. Turbuhaler is preloaded with up to 200 doses of budesonide, formoterol, terbutaline, or other drug. The unique spiral design of the mouthpiece creates turbulent airflow, which breaks the drug agglomerates into mainly small, respirable particles. Desiccant and a cover for Turbuhaler protect the drug from humidity. (Courtesy of AstraZeneca.)

Copyright © 2003 Marcel Dekker, Inc.

and to provide a metered dose, which is predispensed during manufacture of the device.

The Diskus uses the same foiled blisters but in a coiled strip to provide a month's therapy of 60 doses. The premetered design has been shown to provide the optimum in environmental protection and consistent dosing [8]. The blister is filled with micronized drug blended with a lactose carrier, which provides bulk to allow accurate dispensing of drug doses of a few micrograms and separates the fine particles to aid in the dispersion of the respirable dose. When the patient operates the Diskus, the blister presented for the dose is pierced and the powder formulation is aerosolized by the energy of the patient's inhalation. The path length from the blister to the mouth is deliberately short, to minimize drug losses in the device. The powder passes through a single "crucifix" grid to generate the necessary turbulence for efficient dispersion of powder.

B. The Turbuhaler inhaler

Figure 2 is a schematic of the Turbuhaler inhaler. The design concept of this inhaler is to have a bulk reservoir of drug powder, which is dispensed into dosing holes at the point of patient dosing.

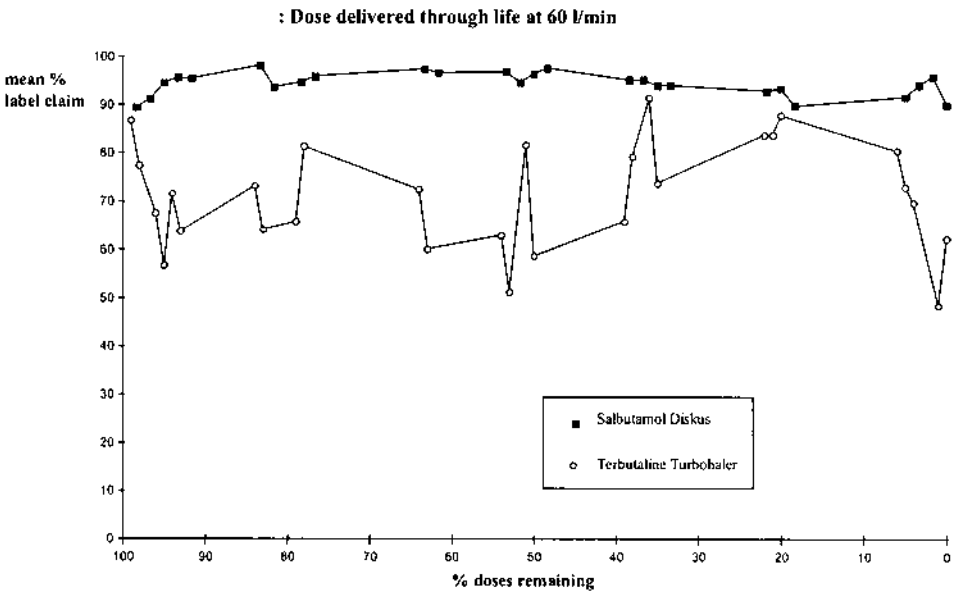


Figure 3 Dosing through life performance of Diskus and Turbuhaler inhalers. (From Ref. [9] courtesy of Lippincott, Williams & Wilkins.)

Copyright © 2003 Marcel Dekker, Inc.

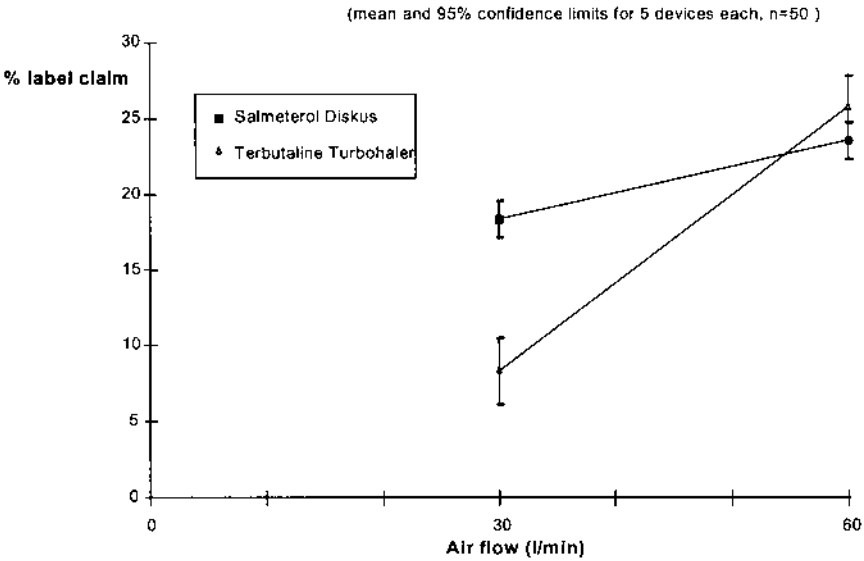


Figure 4 Fine-particle mass results for Diskus and Turbuhaler inhalers. (From Ref. [6] courtesy of Brookwood Medical Publications.)

The powder bed is made up of spheronized, micronized drug in loose aggregates of small particles of pure drug or of a powder blend with lactose. A twisting action on the device by the patient actively feeds the powder aggregate into the dosing holes using scrapers. The design of the scrapers and the dosing holes governs the reproducibility of the dose. Several studies have shown that the small quantities of drug dispensed in this way are less consistent than factory-dispensed doses in the blister pack designs [7]. Figure 3 shows the dosing through life performance of Diskus and Turbuhaler inhalers [9].

The Turbuhaler has a long flow path in the design, with spiral channels to the mouthpiece so that the drug aggregates are broken up by shearing forces. The result is that a relatively high proportion of the emitted drug dose is in respirable particles [10]. Figure 4 shows typical results for the respirable doses emitted from Diskus and Turbuhaler inhalers.

The long flow path in the Turbuhaler contributes to a relatively high airflow resistance of the device, which means that more effort is required by the patient to achieve an acceptable flow rate [11]. Figure 5 shows the dosing performance of Diskus and Turbuhaler inhalers at various flow rates.

Copyright © 2003 Marcel Dekker, Inc.

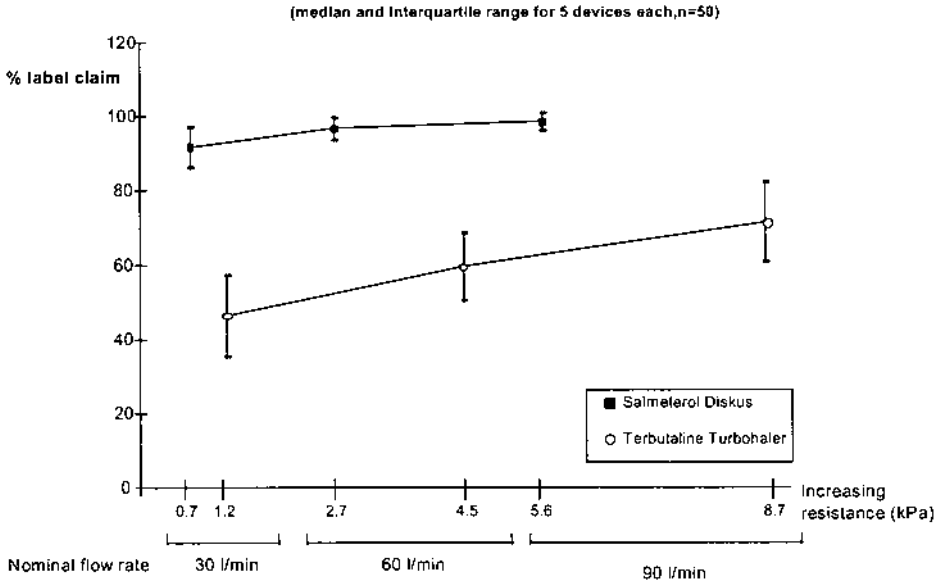


Figure 5 Dosing performance of Diskus and Turbuhaler inhalers at a range of flow rates. (From Ref. [6] courtesy of Brookwood Medical Publications.)

Table 3 Characteristics of Diskus and Turbuhaler Inhalers

Design characteristic	Diskus inhaler	Turbuhaler inhaler
Formulation	Micronized drug with lactose carrier	Pure drug or drug/lactose blend—micronized spheronized aggregates
Dose medium	Single doses in blister strip	Bulk powder reservoir
Dosing mechanism	Premetered in the factory	Volumetric/gravity metering by patient
Number of doses	60	200
Emitted dose consistency	Excellent (RSD $<$ 5%)	Fair (RSD $>$ 25%)
Fine-particle mass (% of loaded dose)	Fair ($<$25%)	Good (up to 45%)
Device resistance	Low	Moderate
Influence of flow rate on emitted dose	Low	Moderate
Influence of flow rate on fine-particle mass	Moderate	High

Copyright © 2003 Marcel Dekker, Inc.

IV. DESIGN CONSIDERATIONS

The major design characteristics of Diskus and Turbuhaler inhalers are summarized in Table 3. Clearly, there is some room for improvement in future devices.

A number of factors contribute to the considerable investment required to develop a new DPI design. Many of the newer devices have multiple components with complex specifications, and may need dedicated production lines to manufacture and assemble them. The drug powder requirements are also highly complex. The drug particles must be presented in the inhalation cloud in a narrow size range (arguably 2–5 μm [12]) to be able to be deposited in the bronchial airways. Manufacture of particles of a few microns requires a process such as micronization, which introduces static charge to the powder and adds a further complication to the problem of dispensing small quantities.

V. ALTERNATIVES TO THE LANDMARK DEVICES

The resistance of a device governs the flow rate generated through it for a given amount of inspiratory effort from a patient. There is an inverse relationship between the resistance and flow rate [13]. The optimum device resistance has not been established, although current pharmacopoeial testing for uniformity of emitted dose is required to be determined at a fixed pressure drop across the inhaler of 4.0 kPa. The DPIs currently available have a range of device resistances, and a number of studies [14] have shown that for some DPIs, dosing performance (in terms of total emitted dose or fine-particle dose) is dependent on the inhalation flow rate generated by the patient. This may be a disadvantage when DPIs are used for treatment of patients with low inhalation flow rates such as patients with chronic obstructive pulmonary disease and young children. Dose consistency and relative flow rate independence of delivery to the lung compatible with the safety and efficacy profile of the drug should therefore be demonstrated for new DPIs. Recently, new multidose-reservoir devices such as the Ultrahaler™ [15] and Clickhaler™ [16] have been assessed for dosing performance at a range of flow rates and have demonstrated comparable performance to Diskus, Turbuhaler, and pMDI.

VI. IN VITRO/IN VIVO CORRELATIONS

Standard pharmaceutical testing of DPIs involves the determination of total emitted dose and fine-particle mass at a range of fixed flow rates. Although this type of testing is suitable for quality control and for comparing performances of different DPIs, it has limited relevance for estimating the performance of an inhalation device when used by a patient. More recently, the use of inhalation simulation

Copyright © 2003 Marcel Dekker, Inc.

machines [17] has provided more realistic in vitro testing by using inhalation profiles recorded from patients and volunteers. The acceleration and deceleration of the airflow through the device as well as the total volume of air may affect the emitted dose and the particle size distribution. The cloud of aerosolized drug is generated from the inhaler using a preprogrammed piston, which draws air through the device following a theoretical or actual inhalation profile. The particle cloud is contained within a chamber and then withdrawn through a collecting device, such as an impactor or impinger, operated at a fixed flow rate. Use of inhalation simulation machines is furthering the understanding of the relationship between the rate of increase of flow rate in an inhalation and the dose output of a DPI [18]. New DPI designs are increasingly being tested using these machines because they can evaluate dosing performance in vitro for a range of simulated patient conditions. Studies comparing DPI performance have also used them to eliminate the inherent variability of in vivo inhalations and, at the same time, to provide a realistic test [19]. However, the factors that determine the deposition of inhaled drugs include both the mode of inhalation and the disease state of the patient's lungs, as well as the aerosol characteristics, which may be largely controlled by design of the DPI. Minimizing the variability associated with the inhalation product [20] is necessary to provide a consistent clinical performance and the desired outcome of clinical effectiveness.

VII. CLINICAL INVESTIGATIONS

Several studies have shown correlations between fine-particle dose, lung deposition, and clinical response [21]. Particle size is a major factor that governs the deposition site in the lung, and the site of action of drugs, such as β_2-agonists and corticosteroids, is being researched [22]. Clinical effectiveness has been demonstrated and comparative doses established for Diskus and Diskhaler Inhalers using fluticasone propionate [23]. Some studies have used different patient inhalation flow rates to correlate clinical response with results from in vitro testing [24]. To establish new DPIs in the market place, clinical effectiveness should be demonstrated at a range of flow rates used by target patient population.

Patient compliance and acceptance should also be established. The next generation of DPIs has a demanding list of requirements. The requirements may be summarized by: efficiency in performance, effectiveness in treatment, and ease of use.

VIII. CONCLUDING REMARKS

Recent years have seen an increase in the development of passive DPIs that has been influenced by the phaseout of chlorofluorocarbon propellants in MDIs. The

Copyright © 2003 Marcel Dekker, Inc.

Diskus inhaler and the Turbuhaler inhaler have been established as landmark devices over this period. Device resistance is an important factor for the development of new DPI devices to ensure that patients with a more compromised respiratory function are able to easily use them. Tools such as inhalation simulation machines have been utilized to enable in vitro/in vivo correlations to be made more readily.

REFERENCES

1. JH Bell, PS Hartley, JSG Cox. Dry powder aerosols. I. A new powder inhalation device. J Pharm Sci 60:1559–1564, 1971.
2. GW Hallworth. An improved design of powder inhaler. Br J Clin Pharmacol 4:689–690, 1977.
3. BS Sumby, KM Churcher, IJ Smith, AC Grant, KG Truman, RJ Marriott, SJ Booth. Dose reliability of the Serevent Diskhaler system. Pharm Tech Int 20–27, June 1993.
4. K Wetterlin. Turbuhaler: a new powder inhaler for administration of drugs to the airways. Pharm Res 5:506–508, 1988.
5. A Brindley, BS Sumby, IJ Smith, D Prime, PA Haywood, AC Grant. Design, manufacture and dose consistency of the Serevent Diskus inhaler. Pharm Tech Eur 7:14–22, 1995.
6. A Malton, BS Sumby, IJ Smith. A comparison of in-vitro drug delivery from two multi-dose powder inhalation devices. Eur J Clin Res 7:177–193, 1995.
7. MT Newhouse, RG Campbell. Evaluation of inter lot variability of the Turbuhaler. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Buffalo Grove, IL: Interpharm Press, 1996, pp. 390–391.
8. D Prime, AL Slater, PA Haywood, IJ Smith. Assessing dose delivery from the Flixotide Diskus inhaler—a multi-dose powder inhaler. Pharm Tech Eur 8:23–36, 1996.
9. A Malton, BS Sumby, Y Dandiker. A comparison of in-vitro drug delivery from salbutamol Diskus and terbutaline Turbuhaler inhalers. J Pharm Med 6:35–48, 1996.
10. H Bisgaard, B Klug, BS Sumby, PKP Burnell. Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma. Eur Respir J 11:1111–1115, 1998.
11. AH de Boer, HMI Winter, CF Lerk. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers. P 1. Inhalation characteristics, work of breathing and volunteers preference in dependence of the inhaler resistance. Int J Pharm 130:231–244, 1996.
12. JJ Sciarra. Pharmaceutical and medicinal aerosols. In: A Herzka, ed. International Encyclopaedia of Pressurized Packaging (Aerosols). London: Pergamon Press, 1966, pp. 571–619.
13. AR Clark, AM Hollingworth. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers. J Aerosol Med 6:99–110, 1993.
14. AH de Boer, D Gjaltema, P Hagedoorn. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers. P 2. Effect of peak flow rate

Copyright © 2003 Marcel Dekker, Inc.

(PIFR) and inspiration time on the in vitro drug release from three different types of commercial dry powder inhalers. Int J Pharm 138:45–56, 1996.
15. K Chippendale. Ultrahaler—design and function. Proceedings: Recent Advances in Dry Powder Inhalers. Management Forum Ltd., London, 1997.
16. M Parry-Billings, RN Boyes, LM Clisby, P Braithwaite, S Williams, AE Harper. Design, development and performance of a multidose dry powder inhaler. Pharm Tech Eur 2:38–46, 2000.
17. PKP Burnell, A Malton, K Reavill, MHE Ball. Design, validation and initial testing of the electronic lung. J Aerosol Sci 29:1011–1025, 1998.
18. PKP Burnell, L Petchey, D Prime, BS Sumby. Patient inhalation profiles and dose emission characteristics from dry powder inhalers. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Buffalo Grove, IL: Interpharm Press, 1996, pp. 314–316.
19. T Small, S Doig, GJ Gibson, B Johal, PKP Burnell, R Jenkins. Use of inhalation profiles from patients with severe obstructive lung disease using the Diskus inhaler and the Turbuhaler inhaler to evaluate device performance exvivo. Eur Respir J 10: 258S, 1997.
20. L Borgstrom, L Asking, O Beckman, E Bondesson, A Kallen, B Olsson. Dose variation within and between individuals with different inhalation systems. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Buffalo Grove, IL: Interpharm Press, 1996, pp. 19–24.
21. SP Newman, F Moren, E Trofast, N Talaee, SW Clarke. Terbutaline sulphate Turbuhaler inhaler: effect of inhaled flow rate on drug deposition and efficacy. Int J Pharm 74:209–213, 1991.
22. PJ Barnes. Beta-adrenergic receptors and their regulators. Am J Respir Crit Care Med 152:838–860, 1995.
23. JI Cater, M Vare, WS Peters. Comparison of the efficacy of fluticasone propionate given twice daily via the Diskus/Accuhaler inhaler and the Diskhaler in patients with asthma. Eur Respir J 8:427S, 1995.
24. KG Nielsen, IL Auk, K Bojsen, M Ifversen, B Klug, H Bisgaard. Clinical effect of Diskus dry powder inhaler at low and high inspiratory flow rates in asthmatic children. Eur Respir J 11:350–354, 1998.
25. IC Ashurst, A Malton, D Prime, B Sumby. Latest advances in the development of dry powder inhalers. Pharm Sci Tech Today 3:246–256, 2000.

Copyright © 2003 Marcel Dekker, Inc.

74

Formulation Challenges: Protein Powders for Inhalation

Hak-Kim Chan
University of Sydney, Sydney, Australia

I. INTRODUCTION

Formulating protein powders for aerosol delivery is a dual challenge as it requires not only flowability and dispersibility of the powders but also biochemical stability of the protein molecules. To satisfy the latter requirement, proteins are usually formulated in amorphous glasses, which, however, are physically unstable and tend to crystallize with interparticulate bond formation and loss of powder dispersibility. In addition, the biochemical stability requirement limits the manufacturing processes that can be used for protein powder production. These challenges, and possible ways to tackle them, will be addressed in this chapter. The issues of microbial risks of proteins and local effects of inhaled powders in the respiratory tract, although important, will not be discussed here.

II. BIOCHEMICAL STABILITY

Proteins have secondary and higher-order structures that must be maintained to be bioactive. During powder production, removal of water from the proteins can cause significant molecular conformational damage, which can lead to further protein degradation such as aggregation, deamidation, and oxidation during storage. Amorphous glassy excipients, mainly carbohydrates, have been widely employed to stabilise proteins for inhalation: e.g., lactose for recombinant human deoxyribonuclease (rhDNase) [1,2], trehalose, lactose, and mannitol for recombinant humanized anti-IgE monoclonal antibody (rhuMAbE25) [3], mannitol and

Copyright © 2003 Marcel Dekker, Inc.

raffinose for insulin [4]. Other suitable excipients may include polymers (e.g., polyvinylpyrrolidone), proteins (e.g., human serum albumin), peptides (e.g., aspartame), amino acids (e.g., glycine), and organic salts (e.g., citrates). Although lactose has been widely used for inhalation products for small-molecule drugs, it may not be suitable for proteins. Being a reducing sugar, lactose is reactive toward the lysine residue, and protein glycation has indeed been observed in both rhDNase and rhuMAbE25 [3,5]. The exact mechanism for protein stabilization in the dry state is debatable. Contributing factors include (a) formation of a glassy state of the protein-excipient system, (b) hydrogen bonding between the excipient and protein molecules, (c) crystallinity of the excipients, and (d) residual water content. In the glassy state, the diffusion rate and mobility of the protein molecules are much less than those in the rubbery state. Thus, any physicochemical reactions leading to protein degradation will be diminished [6]. In contrast to the amorphous excipients, crystalline excipients such as mannitol are known to reduce the stability of proteins [7]. However, mannitol can be used in the amorphous form (e.g., in the presence of glycine) [8]. Evidence for protein stabilization by hydrogen bonding has mainly come from FTIR spectroscopy [9], which provides information on the protein secondary structures. The amide I absorption band ($\sim$1600–1700 cm^{-1}) of freeze-dried proteins with excipients was found to bear more similarities than the freeze-dried proteins alone to the native proteins in an aqueous environment. Water affects the stability of proteins by enhancing the mobility of the protein molecules [10], as shown by solid-state nuclear magnetic resonance spectroscopy [11]. The crystalline or amorphous nature of the excipients is important because it controls the distribution of water between the protein and the excipient in a powder [12].

III. PHYSICAL STABILITY

While glassy materials are desirable for the protein stability, an immediate drawback is their physical instability. Water uptake by fine particles of hydrophilic amorphous materials can be very rapid, owing to the huge specific surface area and high energy state. As exemplified by rhDNase cospray-dried with lactose [1,2], water uptake will induce crystallization, which adversely affects powder dispersibility (Fig. 1).

Lactose at $>$34 wt.% required for the biochemical stability of rhDNase was found recrystallized at moderate storage humidities of 38–57% RH [2]. The probability for a glassy material to crystallize is critically determined by the storage temperature and relative humidity. In the crystallization process water plays an essential role as a plasticizer to lower the Tg ($\sim$10°C decrease per 1% water in sugar-containing formulations), which, when close to the storage temperature, will enhance the molecular mobility required for nucleation [14]. It is thus crucial

Copyright © 2003 Marcel Dekker, Inc.

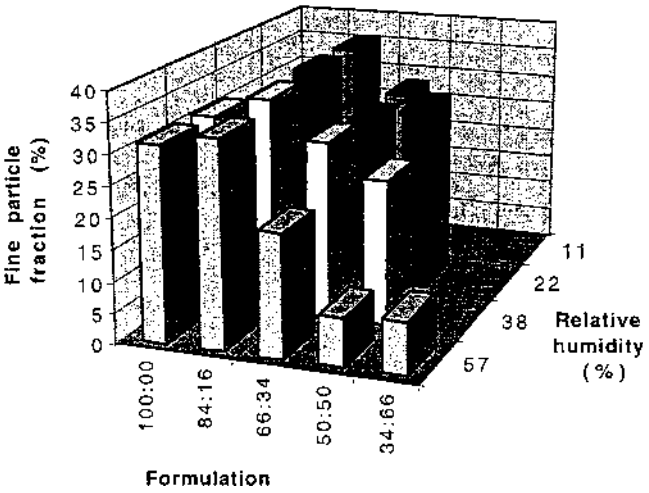


Figure 1 Fine-particle fraction of rhDNase:lactose formulations as a function of protein/sugar content and storage RH after 4 weeks at 25°C. (From Ref. [2], with permission.)

to keep the powder dry to maintain the high Tg, or to use excipients with a high Tg, or to store the powders at a low temperature. It has been proposed to keep fragile glasses 50°C below the Tg to minimize crystallization [13], and this approach would be practical for room temperature storage of materials with a Tg > 70°C. Inhaler devices using gelatin capsules are likely to be problematic since gelatin capsules require a storage humidity of about 50% RH, which may be too high for the glass materials. It is thus no coincidence that aluminum foil blisters have been chosen to store insulin powders for inhalation [15]. It is also important to note that the effect of moisture on powder dispersion can be instantaneous [16]. A possible way to reduce the hygroscopic effect is to use hydrophobic excipients. For example, spray-dried particles of L-isoleucine, a hydrophobic amino acid, were shown to have superior physical stability at 40°C/75% RH for 6 months [17].

IV. DISPERSIBILITY

Powder dispersibility is strongly determined by cohesion, which, in turn, is related to size distribution, bulk density, surface area, surface energy, and surface morphology of the particles. The amorphous form of a given material has higher surface energy and is more hygroscopic, hence more cohesive, than the crystalline

Copyright © 2003 Marcel Dekker, Inc.

one. Dispersibility is thus strongly dependent on the physical state of the powder. Most protein drugs are prepared in the presence of one or more excipients for improved biochemical stability and/or device filling. However, the distribution of protein and excipient(s) in a particle is unlikely to be uniform. When a protein-excipient solution droplet undergoes drying to form a particle, the outer surface tends to be enriched with proteins or macromolecules that are surface active, as compared to small-molecule excipients, which can diffuse rapidly to the particle core. In special cases, small-excipient molecules can crystallize on the particle surface and modify the powder dispersibility [18]. Various formulation approaches can be used to control the dispersibility of protein powders.

A. Use of an Optimal Particle Size

Small particles are cohesive and difficult to disperse; large particles are easier to disperse but are not suitable for inhalation. Small particles can be better dispersed if a high air shear or a high-efficiency inhaler is used. Thus, for a given inhaler at a given airflow, there exists an optimal particle size that will give the maximal fine-particle fraction in the aerosols. The optimal size is expected to be larger for cohesive powders and smaller for less cohesive ones. This was shown for the protein rhDNase (Fig. 2) [18] and the excipient mannitol [19].

B. Co-Spray Drying with a Suitable Excipient

Sugars were used in co-spray-dried anti-IgE antibody dry powder formulations [3]. Lactose had no effect, but both trehalose and mannitol were found to reduce the dispersibility of the antibody when the excipient: protein molar ratio was

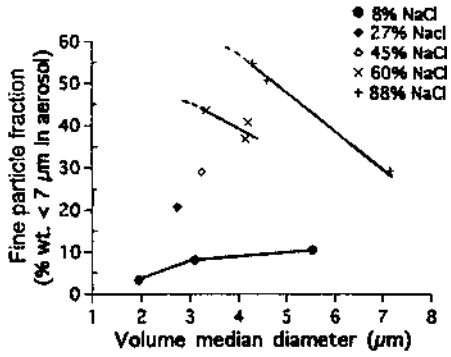


Figure 2 Dispersion properties (as fine-particle fraction) versus particle size for powders of co-spray-dried rhDNase and NaCl. (From Ref. [18], with permission.)

Copyright © 2003 Marcel Dekker, Inc.

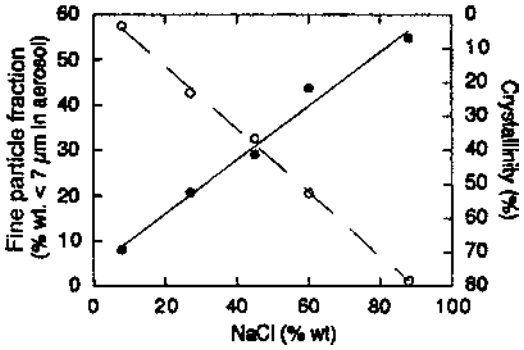


Figure 3 Relationship between NaCl content, the corresponding crystallinity (---), and the dispersibility or fine-particle fraction (—) of rhDNase powder aerosols. [All powders had similar primary particle size distribution before aerosolization, with median diameters of 2.7–3.3 μm (span 1.04–1.63)]. (From Ref. [18], with permission.)

above 200:1. The deleterious effect was attributed to crystallization of the excipients. The choice of excipient is thus critical. Sodium chloride was co-spray-dried with rhDNase to increase the dispersibility. In this particular case, the FPF of rhDNase increased linearly with the NaCl content and powder crystallinity (Fig. 3). Scanning electron microscopy revealed the presence of NaCl crystals on the surface of the protein particles [18]. The dispersibility enhancement can be attributed to decreased cohesion as a result of changes in surface energy and morphology of the crystalline particles when the protein-salt composition changed.

C. Blending with a Suitable Carrier

Blending of the drug with an inert carrier to form a powder mix is generally used to give sufficient quantities for filling of low-dose, potent-protein drugs. However, it can also be explored to manipulate the dispersibility. Blending of spray-dried pure rhDNase with lactose was found to enhance the fine particle fraction (FPF) in the aerosol by a factor of 2 and reduce the device retention 1.5–2 times, leading to a dramatic overall increase of FPF per dose loaded in the inhaler by three- to fourfold (Fig. 4).

In this particular study, the improvement was found to be relatively insensitive to the carrier types, the protein/carrier blend ratio, and the protein particle size [18]. It is interesting to note that although monolayer-like adhesion of the protein particles on the carriers was observed, it did not appear to be a prerequisite for the FPF enhancement. Sometimes blending can reduce the dispersibility as in the case of recombinant human granulocyte–colony stimulating factor blended

Copyright © 2003 Marcel Dekker, Inc.

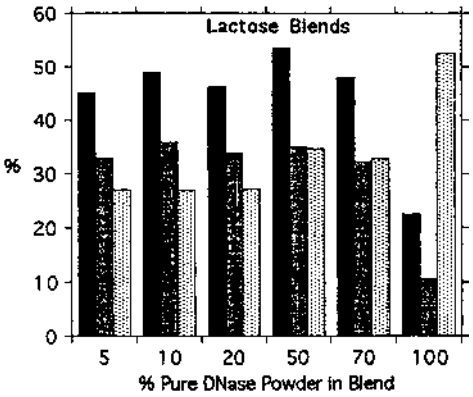


Figure 4 Dispersion properties of lactose blends containing different proportions of pure rhDNase particles (■ fine-particle fraction, ▩ dispersing efficiency, ⊡ device retention) [fine-particle fraction is the wt.% drug < 7 μm in the aerosol, dispersing efficiency is the wt.% drug < 7 μm in the aerosol divided by the drug loaded in the inhaler device, device retention is the wt.% drug retained in the inhaler (and capsules) after dispersion]. (From Ref. [18], with permission.)

with PEG 8000 [20]. More recently, fine carrier particles (<5 μm) have been used to enhance dispersibility [21], but the carrier deposition in the lung may raise clinical and regulatory concerns.

D. Use of Large Porous Particles

Large porous particles (mean diameter 5–20 μm, specific surface area ~50–100 m^2/g) with a high degree of voids (particle mass density < 0.4 g/cc) have been found to improve FPF, as observed in particles containing insulin (20 wt.%) and PLGA (80 wt.%) [22]. Despite the large physical size, the low particle density gave rise to a small aerodynamic size suitable for inhalation. The presence of the polymer also made these particles suitable for controlled release of the protein. The superior aerosol performance of large porous particles was also observed in anti-IgE powders [23] and was attributed to decreased cohesiveness of the porous particles. Further details can be found in the chapter on AIR/Alkermes inhalation technologies.

E. Pulmospheres

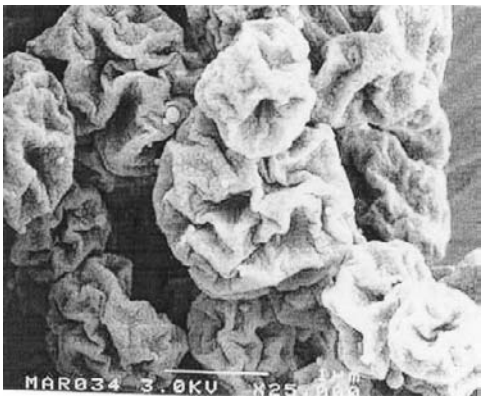
Pulmospheres are hollow, porous particles but smaller in size (3–5 μm), also with low particle density and excellent dispersibility suitable for dry powder in-

Copyright © 2003 Marcel Dekker, Inc.

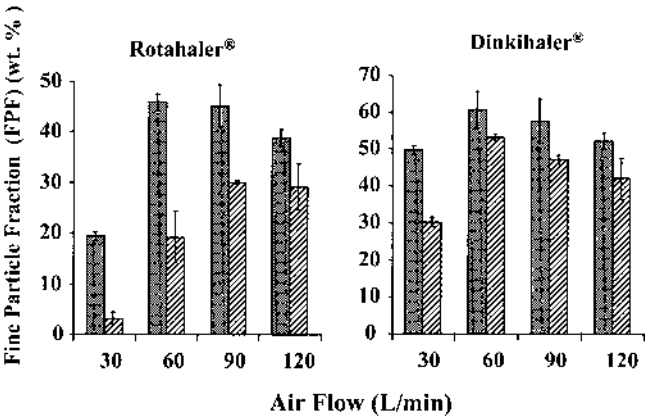
halers. These particles have been used to deliver immunoglobulin to the respiratory tract [24].

F. Use of Wrinkled Particles

Surface morphology can be modified to improve dispersibility. Nonporous solid protein particles with wrinkled surface have recently been reported to give a



(a)



(b)

Figure 5 (A) Scanning electron micrograph of the spray-dried BSA wrinkled particles (scale bar 1 μm). (B) Dispersion properties of ▩ wrinkled versus ▨ smooth spherical particles of BSA at various airflows. (From Ref. [25] with permission, copyright 2000 Serentec.)

Copyright © 2003 Marcel Dekker, Inc.

significant improvement in FPF over nonwrinkled spherical particles of bovine serum albumin (Fig. 5) [25]. A distinct advantage of these particles, like the porous ones, is that they are less dependent on the inhaler device and airflow.

V. METHODS FOR PROTEIN POWDER PRODUCTION

A. Spray Drying

Spray drying is the most commonly used method to prepare protein powders for inhalation, e.g., rhDNase [17] rhGH, tPA [26,27], anti-IgE antibody [3,28], antibodies IgA and IgG [29], insulin [4], and alpha 1-antitrypsin [30].

It involves spraying the protein solution into a concurrent stream of warm air, which evaporates the spray to yield a dry powder that is collected in a cyclone. Depending on the spraying nozzle, powder nature, particle size, and the cyclone collection efficiency, the process yield varies but can be low ($<$50%), which is a major disadvantage of spray drying.

Spraying exposes the protein to mechanical shear and air-liquid interfacial denaturation while hot-air drying subjects the protein to thermal stress and dry-state denaturation. Thus, the major challenge during spray drying is to maintain the protein stability. For rhGH, interfacial denaturation has been shown to cause both soluble and insoluble aggregations, which, in turn, can be suppressed by Zn^{2+} ions and surfactant polysorbate 20, respectively [26,27]. Combination of polysorbate 20 and Zn^{2+} effectively reduced the total aggregation to 1.5% [27]. While the stabilizing action of Zn^{2+} is specific to rhGH by forming a $(rhGH\text{-}Zn^{2+})_2$ dimer, the use of surfactants should generally be applicable to other proteins that are vulnerable to air-liquid interfacial denaturation.

Spray drying is not limited to aqueous solutions and nonaqueous systems have been used. Ethanolic solutions (87%) of insulin containing human serum albumin and dipalmitoyl phosphatidylcholine (DPPD) as excipients were spray-dried to prepare large porous particles for sustained release [31]. Mixtures comprising a hIgG solution and a fluorocarbon-in-water emulsion were spray-dried to obtain lipid-based hollow porous microspheres (Pulmospheres™) of human IgG. The spray-dried powders were collected in perflubron and lyophilized to produce free-flowing particles [24].

B. Spray Freeze Drying

Spray freeze drying involves spraying the protein solution into a freezing medium (usually liquid nitrogen) followed by lyophilization. The method has recently been applied to prepare rhDNase and anti-IgE antibody particles for inhalation [23]. Compared with spray drying, this process produces light and porous particles with superior aerosol performance, and the production yield is almost 100%.

Copyright © 2003 Marcel Dekker, Inc.

However, this process is more costly and time consuming as it requires the additional use of liquid nitrogen and freeze drying.

C. Double-Emulsification Solvent Evaporation

This method was used to produce large porous particles of PLGA particles loaded with 20 wt.% insulin [22]. Aqueous insulin solution was sonicated with methylene chloride solution of PLGA to form the first emulsion, which was then poured into 1% aqueous polyvinyl alcohol solution and homogenized to form the double emulsion. The major disadvantage of this method is exposing the proteins to shear or sonic stress and organic solvents during emulsification. It is also a more complicated procedure than spray drying.

D. Lyophilization/Milling

This is a two-step process involving protein lyophilization followed by milling. Gas-jet milling has been employed to micronize lyophilized powders of human growth hormone, interferon-beta, and granulocyte-colony-stimulating factor [32]. However, milling produced insoluble contaminants and protein inactivation. Thus, abrasive-resistant mills utilizing high-purity nitrogen and milling stabilizers such as human serum albumin and sorbitol were required. Protein degradation as well as high energy and time demands limit the general usefulness of this process.

E. Solvent Precipitation

Inhalable protein particles can be obtained by precipitation from aqueous solutions using nonsolvents. In recent years, supercritical fluids (SCFs) are increasingly used for this application. Carbon dioxide is particularly attractive as it has a low critical temperature of 31.1°C for operation. It is also nontoxic, inexpensive, and readily available. However, being nonpolar and immiscible with water, supercritical CO_2 cannot be readily used as an antisolvent to precipitate proteins from aqueous solutions. Insulin precipitated from DMSO solutions has been shown structurally stable for 2 years' storage [33]. However, DMSO is toxic and residual solvent can be a major concern. To overcome this limitation, water-based protein solutions can be used. York and co-workers have used a special coaxial nozzle to enhance mixing of water-based protein solution with supercritical CO_2 [34]. Alternatively, fine powders can be obtained by expanding an emulsion of the aqueous protein solution and supercritical CO_2 through a nozzle [35]. More recently, Foster and co-workers developed another approach by using high-pressure CO_2 modified with ethanol, which has successfully been employed as an antisolvent to precipitate rhDNase and insulin from aqueous solutions [36,37]. A poten-

Copyright © 2003 Marcel Dekker, Inc.

tial problem of using CO_2 is its acidic nature, but solution pH can be adjusted to minimize protein degradation.

VI. CONCLUSIONS

Formulation of proteins as powders for aerosol delivery is a dual challenge as it requires both powder dispersibility and protein biochemical stability. However, a balance between these two requirements can be found and a number of proteins have successfully been formulated. Selection of appropriate excipients and minimization of powder exposure to moisture are critical as they affect both physical and biochemical stabilities. Currently, protein powders are mainly produced by spray drying, but other technologies such as supercritical fluid precipitation may prove to be useful alternatives in the future.

REFERENCES

1. H-K Chan, Gonda I. Solid state characterization of spray-dried powders of recombinant human deoxyribonuclease (rhDNase). J Pharm Sci 87:647–654, 1998.
2. AR Clark, N Dasovich, I Gonda, H-K Chan. The balance between biochemical and physical stability for inhalation protein powders: rhDNase as an example. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Buffalo Grove, IL: Interpharm Press, 1996, pp. 167–174.
3. JD Andya, Y-F Maa, HR Costantino, P-A Nguyen, N Dasovich, T Sweeney, CC Hsu, SJ Shire. The effect of formulation excipients on protein stability and aerosol performance of spray-dried powders of a recombinant humanized anti-IgE monoclonal antibody. Pharm Res 16:350–358, 1999.
4. JS Patton, L Foster, RM Platz. Methods and compositions for pulmonary delivery of insulin. US patent 5,997,848, 1999.
5. CP Quan, N Dasovich, C Hsu, T Patapoff, E Canova-Davis. Susceptibility of rhDNase I to glycation in the dry-powder state. Anal Chem 71:4445–4454, 1999.
6. F Frank. Long-term stabilization of biologicals. Biotechnology 12:253–256, 1994.
7. K Izutsu, S Yoshioka, T Terao. Decreased protein-stabilizing effects of cryoprotectants due to crystallization. Pharm Res 10:1232–1237, 1993.
8. MJ Pikal, KM Dellerman, ML Roy, RM Riggin. The effects of formulation variables on the stability of freeze-dried human growth hormone. Pharm Res 8:427–436, 1991.
9. JF Carpenter, SJ Prestrelski, A Dong. Application of infrared spectroscopy to development of stable lyophilized protein formulations. Eur J Pharm Biopharm 45:231–238, 1998.
10. MJ Hageman. Water sorption and solid-state stability of proteins. In: TJ Ahern, MC

Copyright © 2003 Marcel Dekker, Inc.

Manning, eds. Stability of Protein Pharmaceuticals. Part A. New York: Plenum Press, 1992, pp. 273–309.
11. F Separovic, YH Lam, X Ke, H-K Chan. A solid-state NMR study of protein hydration and stability. Pharm Res 15:1816–1821, 1998.
12. H-K Chan JK-L Au-Yeung, I Gonda. Development of a mathematical model for the water distribution in freeze-dried solids. Pharm Res 16:660–665, 1999.
13. B Hancock, S Shamblin, G Zografi. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. Pharm Res 12:799–806, 1995.
14. Y Roos, M Karel. Plasticizing effect of water on thermal behavior and crystallization of amorphous food models. J Food Sci 56:38–43, 1991.
15. JS Patton. Deep-lung delivery of therapeutic proteins. Chem Tech December:34–38, 1997.
16. NYK Chew, H-K Chan. Effect of humidity on the dispersion of dry powders. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 615–617.
17. C Yamashita, T Nishibayashi, S Akashi, H Toguchi, M Odomi. A novel formulation of dry powder for inhalation of peptides and proteins. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Buffaloa Grove, IL: Interpharm Press, 1996, pp. 483–485.
18. H-K Chan, A Clark, I Gonda, M Mumenthaler, C Hsu. Spray dried powders and powder blends of recombinant human deoxyribonuclease (rhDNase) for aerosol delivery. Pharm Res 14:431–437, 1997.
19. NYK Chew, H-K Chan. Dispersion of mannitol powders as aerosols: influence of particle size, air flow and inhaler device. Pharm Res 16:1098–1103, 1999.
20. DL French, DA Edwards, RW Niven. The influence of formulation on emission, deaggregation and deposition of dry powders for inhalation. J Aerosol Sci 27:769–783, 1996.
21. P Lucas, K Anderson, JN Staniforth. Protein deposition from dry powder inhalers: fine particle multiplets as performance modifiers. Pharm Res 15:562–569, 1998.
22. DA Edwards, J Hanes, G Caponetti, J Hrkach, A Ben-Jebria, ML Eskew, J Mintzes, D Deaver, N Lothan, R Langer. Large porous particles for pulmonary drug delivery. Science 276:1868–1871, 1997.
23. Y-F Maa, P-A Nguyen, T Sweeney, SJ Shire, CC Hsu. Protein inhalation powders: spray drying vs spray freeze drying. Pharm Res 16:249–254, 1999.
24. AI Bot, TE Tarara, DJ Smith, SR Bot, CM Woods, JG Weers. Novel lipid-based hollow-porous microparticles as a platform for immunoglobulin delivery to the respiratory tract. Pharm Res 17:275–283, 2000.
25. NYK Chew, H-K Chan. Effect of particle size and surface morphology on the dispersion of albumin powders. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 619–622.
26. M Mumenthaler, CC Hsu, R Pearlman. Feasibility study on spray-drying protein pharmaceuticals: recombinant human growth hormone and tissue-plasminogen activator. Pharm Res 11:12–20, 1994.
27. Y-F Maa, P-A Nguyen, SW Hsu. Spray-drying of air-liquid interface sensitive recombinant human growth hormone. J Pharm Sci 87:152–159, 1998.
28. HR Costantino, JD Andya, P-A Nguyen, N Dasovich, T Sweeney, SJ Shire, CC

Copyright © 2003 Marcel Dekker, Inc.

Hsu, Y-F Maa. Effect of mannitol crystallization on the stability and aerosol performance of a spray-dried pharmaceutical protein, recombinant humanized anti-IgE monoclonal antibody. J Pharm Sci 87:1406–1411, 1998.
29. RM Platz, JS Patton, L Foster, M Eljamal. Dispersible antibody compositions and methods for their preparation and use. US patent 6,019,968, 2000.
30. M Eljamal, JS Patton. Methods and apparatus for pulmonary administration of dry powder α1-antitrypsin. US patent 5,993,783, 1999.
31. R Vanbever, JD Mintzes, J Wang, J Nice, D Chen, R Batychy, R Langer, DA Edwards. Formulation and physical characterization of large porous particles for inhalation. Pharm Res 16:1735–1741, 1999.
32. RM Platz, A Ip, CL Whitham. Process for preparing micronized polypeptide drugs. US patent 5,354,562, 1994.
33. MA Winters, PG Debenedetti, J Carey, HG Sparks, SU Sane, TM Przybycien. Long-term and high-temperature storage of supercritically-processed microparticulate protein powders. Pharm Res 14:1370–1378, 1997.
34. R Sloan, HE Hollowood, GO Hupreys, W Ashraf, P York. Supercritical fluid processing: preparation of stable protein particles. Proceedings of the 5th Meeting of Supercritical Fluids, Nice, France, 1998.
35. RE Sievers, SP Sellers, KD Kusek, GS Clark, BJ Korte. Fine-particle formation using supercritical carbon dioxide-assisted aerosolization and bubble drying. Proceedings of 218th ACS National Meeting, New Orleans, 1999.
36. R Bustami, H-K Chan, NR Foster. Aerosol delivery of protein powders processed by supercritical fluid technology. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VII. Raleigh, NC: Serentec Press, 2000, pp. 611–613.
37. R Bustami, H-K Chan, F Dehaghani, NR Foster. Generation of micro-particles of proteins for aerosol delivery using high pressure modified carbon dioxide. Pharm Res 17:1360–1366, 2000.

Copyright © 2003 Marcel Dekker, Inc.

75

The Development of Large Porous Particles for Inhalation Drug Delivery

Richard Batycky, Daniel Deaver, Sarvajna Dwivedi, Jeffrey Hrkach, Lloyd Johnston, Tracy Olson, and James E. Wright
Alkermes, Inc., Cambridge, Massachusetts, U.S.A.

David Edwards
Harvard University, Cambridge, Massachusetts, U.S.A.

I. INTRODUCTION

Prior to publication in the journal *Science* [1], the idea of inhaling spherically isotropic therapeutic particles into the lungs with geometric sizes greater than 5 μm was not pursued under the impression that such particles deposit excessively in the head and inhalation device [2–5]. We have found, however, that this nontraditional mode of pulmonary drug delivery is actually more efficient than the traditional method, particularly should the large particles possess densities sufficiently small to create aerodynamic particle sizes in the range of 1–5 μm, and for deep-lung delivery, 1–3 μm [6–8]. Our findings to date comprise results from in vitro, animal, and human testing of therapeutic molecules such as albuterol sulfate [9] for asthma and insulin [10] for diabetes; they include drugs ranging from large hydrophilic molecules such as monoclonal antibodies, to small lipophilic molecules such as estradiol [8]. We review in this chapter the primary elements of porous particle inhalation technology as currently developed at Alkermes. We describe the formulation, aerosol science, manufacturing, and toxicological testing of porous powders, and follow this with a brief discussion of inhaler delivery.

Copyright © 2003 Marcel Dekker, Inc.

II. FORMULATING POROUS PARTICLES FOR FLEXIBLE DRUG DELIVERY

Large porous particles can be useful vehicles for the sustained delivery of drugs to the lungs, for reasons briefly described below. They can also be useful for delivery of drugs rapidly into the lungs or bloodstream, potentially at relatively high drug doses, for reasons described in the following section. Prepared in dry powder form, they can finally be designed to provide room-temperature stability. This breadth of potential carries with it formulation challenges that demand flexibility, particularly in terms of porous particle composition. Using a spray-drying process described later, we seek to prepare large porous particles, for current applications, as mixtures of pharmaceutical excipients and drug (see Fig. 1). Both drug and excipients are distributed throughout the porous particle matrix at ratios chosen to meet the targeted drug dose, drug stability, and drug release kinetics. Drug fractions ranging from less than 1% by weight to nearly 100% have been achieved in formulations prepared to date. Given that excipient clearance from the lungs is an important concern, we ideally choose excipients that are either endogenous to the human lung or approved for pulmonary or other routes of delivery to humans. Examples of excipients in each class include the lung lipid dipalmitoyl phosphatidylcholine (dppc) and the sugar lactose [7,9].

Drug choice obviously greatly influences excipient selection. Currently we develop large porous particle formulations of small molecules, such as albuterol sulfate for asthma, and large proteins such as growth hormone for growth hor-

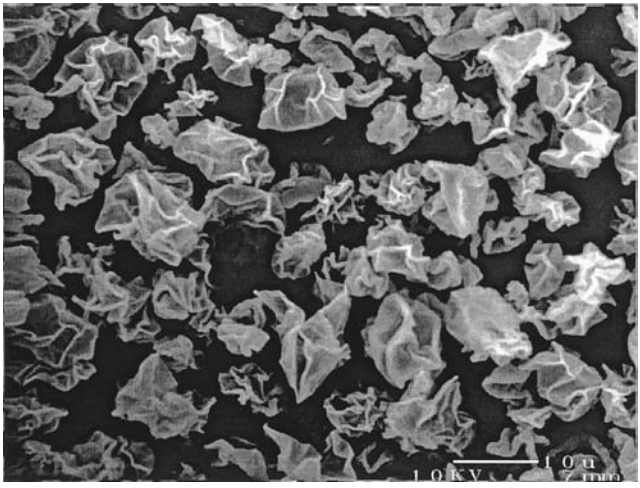


Figure 1 Scanning electron micrograph of large porous particles.

Copyright © 2003 Marcel Dekker, Inc.

mone deficiency. The chemistry of each of these drugs will dictate a different solid state with each excipient matrix, impacting on particle morphology and shelf-life stability. It will also influence the kinetics of particle dissolution and drug release in the lungs.

Particle chemistry also determines the ability to achieve sustained release of drugs through the physical and chemical integrity of the particle matrix. Sustained-release formulations require relatively insoluble particle matrices that release drugs over prolonged periods of time. Equally important as particle chemistry for pulmonary drug delivery is particle size, since standard (small nonporous) particles are cleared soon after deposition in the lungs by mucociliary action in the airways and macrophage uptake in the alveolar region of the lungs. Large porous particles have the potential to avoid phagocytic clearance in the peripheral regions of the lungs, thus prolonging the duration of meaningful sustained drug delivery [1,8,9].

For a variety of reasons related to excipient choice and practicality, we currently develop our sustained-release pulmonary formulations with release times up to about a day. We also research delivery matrices for longer times. Formulation factors influencing drug release from the particle matrix include drug load, water uptake by the particle, particle matrix integrity, drug distribution within the particle, and specific excipient-drug interactions.

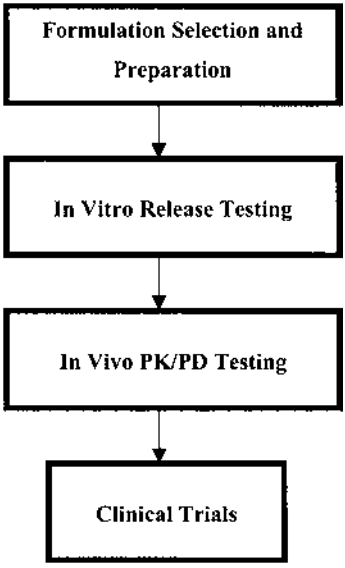


Figure 2 Pathway to sustained-release formulation development at AIR/Alkermes.

Copyright © 2003 Marcel Dekker, Inc.

After initial ranking of release rates in vitro, using specialized methods that simulate the environment of the human respiratory tract, promising candidates are administered to small animals, with techniques described later in this chapter, to assess in vivo pharmacokinetic and/or pharmacodynamic profiles. Iteration is often necessary between in vitro and in vivo screening, and such iteration leads to a better appreciation of the utility of each in vitro tool. For instance, such internal testing has shown that traditional USP paddle systems are unsuited for ascertaining the release profiles that may be expected in the pulmonary space. Upon evaluation of the in vivo data, together with the in vitro data, successful candidates may be moved into human clinical trials (see Fig. 2).

III. AEROSOL PARTICLE PHYSICS

Dry powders of respirable drug particles (i.e., aerodynamic size 1–5 μm) are traditionally difficult to deliver in a deaggregated state to the lungs since interparticle adhesion forces, such as elecrostatic and van der Waals forces, promote particle–particle aggregation in the initial dry powder. To overcome such forces, inhalers can be designed to deliver sufficient power to overcome these interparticle forces and effectively disperse the particles for inhalation. A major advantage of large porous particles lies in the fact that they disperse far more easily than standard nonporous particles of similar aerodynamic diameter; thus they can be effectively dispersed even from relatively simple inhaler systems.

To understand why large porous particles aerosolize more easily than small nonporous particles, in the absence of large pharmaceutically inert "carrier particles" and for the same drug loading per particle, consider the case of particles adhered by van der Waals attractive forces (similar arguments can be made for electrostatic interactions). The van der Waals attractive force (f) holding any two atoms together [11] is given by:

$$f = 6C/r^7 \tag{1}$$

where C is a coefficient of the atom–atom pair potential. This pair potential can be integrated over two adjacent particles to obtain a particle–particle attractive force (F_a). For two identical spherical particles of envelope or geometric diameter D_g and surface material density ρ_s, this attractive force is given by

$$F_a = \alpha\rho_s^2 D_g \tag{2}$$

where $\alpha = \pi^2 C/24z^2M_w^2$, with z the separation distance between the two particles and M_w the molecular weight of the atoms comprising the particles. That is, the force holding any two particles together *increases* proportionally with their diameter. In dry powder inhalers, the dispersive force (F_d) required to overcome F_a

Copyright © 2003 Marcel Dekker, Inc.

is provided by a linear air shear field,* and grows proportionally with the *square* of distance between particle centers. For spherical particles of diameter D_g, this gives

$$F_d = \pi\mu G D_g^2 \tag{3}$$

where G is the air shear rate and μ the air viscosity. Deaggregation of a particle occurs when $F_a/F_d < 1$, and, by extension, deaggregation of N particles in a powder occurs when $NF_a/F_d < 1$. The number N of particles in a powder of mass m is given by

$$N = 6m/\pi\rho_e D_g^3 \tag{4}$$

where ρ_e is the envelope particle density. Note that while ρ_e and ρ_s are identical for a perfectly homogeneous particle, ρ_s expresses the particle density in the immediate vicinity of the particle contact surface, and ρ_e the overall envelope particle density.

Combining the above formulas shows that deaggregation of a dry powder of identical spherical particles will occur when

$$\alpha\rho_s^2 6m/\pi\rho_e\pi\mu G D_g^4 < 1 \tag{5}$$

This result reveals two important trends and underlies the utility of large porous particles as pulmonary delivery vehicles.† First, for two powders of identical mass and identical density, dispersion of the powders will increase in ease with the *inverse fourth power of the geometric diameter*. Alternatively, for two powders of identical mass and identical aerodynamic diameter (but different geometric diameter), dispersion of the powders will increase in ease with the *inverse square power of the geometric diameter* (i.e., note that the square of aerodynamic diameter equals $\rho_e D_g^2$). This means that, given two powders with particles of the same aerodynamic but different geometric sizes, say 3 μm and 12 μm, 16 times less energy is required to disperse the same mass of 12-μm particles than to disperse 3-μm particles. Conversely, should an inhaler shear field exert just sufficient energy to disperse a porous powder of 12-μm diameter particles, a nonporous powder of 3-μm diameter particles (of similar aerodynamic diameter) will tend to disperse into aggregates of roughly 12-μm diameter, i.e., particles that are four times the aerodynamic size of the large porous particles, and therefore

* The assumption of linearity assumes the particles to be much smaller than the characteristic dimension of the shear field, or inhaler orifice. For instance, Alkermes' porous particles (AIR™) are typically 10 μm in diameter, and inhaler orifice dimensions on the order of millimeters.

† Another trend implicit to Eq. (1) includes the role of surface roughness. Note that increasing surface roughness corresponds to diminishing surface material density (ρ_s), which also promotes diminished particle–particle aggregation. As increasing surface roughness leads to diminishing envelope particle mass density [7], surface roughness can be viewed as a useful contributing parameter to the efficacy of porous particle technology.

Copyright © 2003 Marcel Dekker, Inc.

be unlikely to enter the lungs. Another interesting calculation involves the idea of small porous particles, advocated elsewhere [12]. Imagine, two powders with porous particles of the same low envelope density (say, 0.06 g/cm^3) but different geometric sizes, say 3 μm and 12 μm. The aerodynamic size of these respective aerosol particles is therefore 0.7 and 2.9 μm. From Eq. (1) we see that 256 times less energy is required to disperse the same mass of 12-μm particles than to disperse 3-μm particles. Should an inhaler shear field again exert just sufficient energy to disperse a powder of 12-μm-diameter porous particles, an aerosol of 3-μm-diameter porous particles, in this same shear field, will tend to disperse into aggregates of roughly 12-μm diameter, i.e., particles with an aerodynamic diameter *sufficient to enter and deposit in the lungs*. Thus, small porous particles can be aerosolized easily into the lungs as large porous particle aggregates. However, since the aggregate size is a finely sensitive function of the force of dispersion, small porous particle delivery to the lungs will be inherently flow-rate-dependent and therefore less desirable as a mode of pulmonary drug delivery.

The theoretical concept described above is demonstrated in the results summarized in Figure 3. Here, two powders, containing porous (AIR) particles of 10 and 12 μm mean geometric diameter, are dispersed in a RODOS dry powder disperser (Sympatec, Princeton, NJ) and particle size of the emitted aerosol is measured by laser diffraction. The geometric size of the emitted aerosol is first evaluated at a disperser shear rate of 4 bar, and then all particle sizes are reported normalized relative to this number, providing a "normalized" geometric size of the emitted aerosol. As can be seen, large porous powders emit at essentially

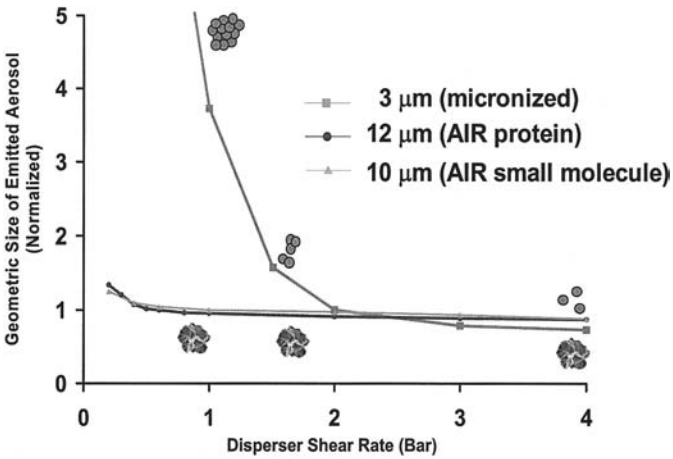


Figure 3 Normalized geometric size of three different powders in the RODOS system at a range of disperser shear rates.

Copyright © 2003 Marcel Dekker, Inc.

their primary (i.e., 4-bar) size down to very low shear rates, whereas a 3-μm micronized albuterol sulfate powder exhibits significant aggregation at shear rates below 2 bar.

The ease of dispersibility of large porous particle powders leads to a number of advantages relative to small nonporous particle powders. First, since a relatively small amount of energy is required to aerosolize a given mass of powder, relatively large masses of powder (greater than 25 mg) can be aerosolized into the lungs in a single breath. Second, the requirement of low inhaler energy permits the use of a simple, cost-effective inhalation device. And third, unlike with small particles (porous or nonporous), the particle size distribution of dispersed large porous particles can exhibit little flow-rate dependence over a wide range of inhalation flow rates.

IV. MANUFACTURING OF LARGE POROUS PARTICLES

Currently we manufacture, fill, and package large porous particle formulations for research testing, toxicology studies, and clinical evaluation. In this section we briefly review these processes.

The clinical performance of porous particle inhalation products is primarily related to the physical characteristics of the particles. To ensure good and repeatable clinical performance of the product, the bulk powder manufacturing process must consistently produce particles to fairly tight and demanding specifications. In addition to tight controls on geometric and aerodynamic particle size, it is also important to preserve the particle morphology, which can be challenging during scale-up of the bulk powder process.

Among the different techniques for producing large porous particles (e.g., double emulsification and supercritical fluid processing), we choose to pursue spray drying to produce our formulations for reasons of robustness, ease of scale-up, and cost. There are three basic unit operations in the spray-drying process: solution preparation, spray drying, and powder collection. In the first step, active drug and excipients are prepared in an aqueous or organic solvent or in a cosolvent mixture. The spray-drying solution is then pumped at a controlled rate to the spray dryer where it is atomized into fine droplets using a rotary atomizer. The atomizer produces a near-uniform spray of fine droplets that is contacted by hot gas introduced at a controlled temperature above the atomizer. The hot gas evaporates the solvent from the droplets leaving a solid particle. The hot gas may be either air or nitrogen, depending on the nature of the feed solution. The solid particles then exit the spray dryer in a gas stream and are separated in the product collection operation. Ideally, all the particles are recovered with this collection system, though practical losses to dryer walls and piping invariably prevent a perfect 100% product yield. As would be the case with other spray-dried products,

Copyright © 2003 Marcel Dekker, Inc.

yields greater than about 90% are sought for all our porous particle formulations. We have successfully used both cyclones and baghouses to collect porous particles. The basic difference between these two collection systems is that a cyclone collects particles based on centrifugal force while the baghouse uses the principle of filtration. Details of cyclone and baghouse design are available elsewhere [13,14]

Porous powders have very low bulk density and aerosolize quite easily. These properties lead to interesting challenges with bulk material transport and filling operations. In particular with filling, the most common method of dose filling (constant volume) is potentially problematic since porous powders exhibit a large difference between bulk and packed density. Packing the powder into a constant volume chamber can, however, be achieved by a variety of methods, including mechanical force (tamping), vacuum, gas flow, vibration, gravity, or a combination of these. In general, the higher the compressive force applied to the powder, the more consistent a density is achieved, which leads to more accurate dosing.

Finally, since moisture can adversely affect dry powder inhalation products, controlled handling of powder and, ultimately, packaging is required to protect the product from the environment. Blister packing, using either polymeric, aluminum, or a combination of these materials, can be an effective moisture barrier as well as a light barrier for light-sensitive materials. For capsule-based inhalation products, the use of cellulose capsules as opposed to gelatin capsules is advantageous because of the low water content of the cellulose capsules (1–5% water as opposed to the 14–16% water content for gelatin capsules). Environmental controls in the filling and packaging manufacturing areas are required as the ambient environment is what is sealed into the product. Thus, if a dry product is needed, the filling and packaging environments need to be dry. Isolator technology can be used to enclose filling and packaging operations to more economically achieve the desired environments than strict environmental control of large processing rooms.

V. TOXICOLOGICAL TESTING OF LARGE POROUS PARTICLES

Preclinical evaluation of pharmaceutical products for pulmonary delivery is critical for determining the potential for clinical efficacy and ensuring safety of the product. Conventional dry powders are frequently administered to animals using methodologies initially designed for studying environmental pollutants. These traditional methods of aerosol generation have not been very effective for toxicological studies of large porous particles owing to their highly aerosolizable nature, as described previously in this chapter. Consequently, we have developed novel

Copyright © 2003 Marcel Dekker, Inc.

strategies for particle delivery to various animal models. For acute dosing of rodents, an intratracheal dry powder insufflation method has provided reproducible delivery to the airways and alveolar lung regions. In larger species, forced inhalation procedures via endotracheal intubation or nose-only mask exposure can be used to efficiently deliver large porous particles to the lungs. By using these methods in conjunction with in vitro powder characterization methods, we have successfully examined early pharmacokinetics (PK), pharmacodynamics (PD), and safety of large porous particles for pharmaceutical products. For long-term repeated administration of dry powders to large animals, such as dogs and monkeys, we have developed, with partner contract research organizations, repeated-dosing strategies involving the generation of bursts of aerosols.

Using one or more of these delivery systems, we perform pharmacodynamic evaluation of respiratory functions to study formulations designed for the treatment of asthma and chronic obstructive pulmonary disease (COPD), particularly. Moving away from classic methods of strain-gauge plethysmography or mechanical ventilation, we currently use noninvasive, nonrestraining whole-body plethysmography (Buxco Plethysmography Systems, Troy, NY) that can be performed repeatedly on the same animal, providing a wide array of flow- and volume-derived ventilatory parameters. Bronchoprovocative agents (methacholine, histamine) elicit changes in pulmonary function parameters associated with airway reactivity [peak expiratory flow, pause, enhanced pause (PenH)], which provide useful pharmacodynamic markers of the biological effectiveness of porous powder formulations. When using intratracheal insufflation, the sensitivity of the plethysmography system allows Alkermes to test the effectiveness of low amounts of active drug substance ($<$1.0 μg) while administering as little as 250 μg of a drug-containing formulation. We also use two bronchoprovocative models (rats and guinea pigs with methacholine or histamine challenge). Guinea pigs represent a highly sensitive model with a steep dose-response to bronchoprovocative agents. However, rats are less sensitive to methacholine and histamine allowing for identification of shifts in the airway reactivity dose-response curve that are indicative of bronchoprotection. These animal models and airway reactivity tests provide valuable indicators of the efficacy of pharmaceutical agents targeted at the prevention of bronchoconstriction (treatments for asthma, chronic obstructive pulmonary disease, or acute respiratory distress syndrome). In addition, a variety of animal models of pulmonary disease (ovalbumin-induced asthma, bleomycin-induced fibrosis, elastase-induced emphysema) can be developed and the efficacy of therapeutic agents can be tested. These pulmonary function screening methods can provide valuable insight in formulation development and enhance decision making in clinical testing regimens.

We perform PK evaluation of porous powders for most of our formulations, especially those aimed at delivery of drug to the systemic circulation. When the active drug substance is a peptide or protein, alveolar deposition will have a

Copyright © 2003 Marcel Dekker, Inc.

major impact on the ability of the drug to reach the systemic circulation. For these applications especially, intratracheal insufflation provides a simple and reproducible method for dosing rodents to achieve maximum lung deposition. We have found that consistent results can be achieved in Spragrue-Dawley rats (350–400 g) in terms of T_{max}, C_{max}, area under the curve, and bioavailability when animals are insufflated with as little as 100 μg of powder, with the upper range being approximately 5000 μg.

Toxicity and safety screening of pharmaceuticals is an important concern, notably with excipients or drugs that have not been studied in the pulmonary system. Our goal has been to screen potential formulations by using dosing methods that allow for high levels of pulmonary deposition. As cited above, intratracheal insufflation has provided an extremely useful tool in screening procedures when used in conjunction with collection of bronchoalveolar lavage fluid (BAL). Typically powders are administered at three doses, with the highest dose of powder representing the maximum amount of material that can be delivered using the insufflation technique. Twenty-four hours after dosing, BAL fluid is collected and analyzed for total cell number, differential cell counts, total protein, and other biochemical markers indicative of inflammation and cell damage. We have observed a good correlation between formulations that cause acute inflammation in rats using this approach, and histopathological lesions observed during examinations of pulmonary tract tissues at necropsy.

VI. INHALER DEVELOPMENT FOR LARGE POROUS PARTICLES

Given the advantages inherent in large geometric size (discussed previously), we can design inhalers to achieve high aerosolization efficiency with a simple dispersion mechanism. This permits a range of features related to drug types, dose ranges, dosing regimens, and usage scenarios, and in principle enables the development of a versatile family of inhalers to meet the needs of a wide range of pulmonary products while consistently delivering high performance (Fig. 4).

Our current inhalers utilize a capsule-based dispersion chamber that consists of a simple cylinder through which air permeates on inhalation. The chamber promotes dispersion of the large porous powders without impellers, motors, or other external energy sources. It is breath-activated and delivers porous powders from preloaded standard-size cellulose or plastic capsules. During use, a capsule is loaded into the chamber and punctured. When the patient breathes, air enters the chamber tangentially, creating a strong internal vortex, which consistently empties the capsule. The turbulent airflow in the chamber ensures complete dispersion of the powder exiting the capsule. The spinning action of the capsule also creates a clear signal to verify delivery of the powder to the respiratory tract.

Copyright © 2003 Marcel Dekker, Inc.

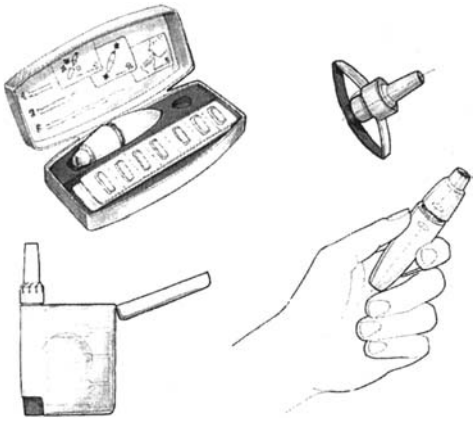


Figure 4 The Alkermes family of inhalers.

With conventional dry powder inhalers, the carrier excipient powders constitute the majority of the inhaled powder mass. Even when carrier particles are not used, the particles are relatively dense, small, and highly cohesive, and are therefore not easily dispersed. With large porous powders, carrier powders are not needed, and since the particles are inherently dispersible over a range of flow rates, these inhalers can deliver from small to large drug masses without any particular inhaler design change. Drug masses from a few micrograms to several tens of milligrams can be delivered in a single breath by varying particle drug content and capsule fill weight. Another advantage of avoiding carrier powder in the formulation is that relatively little powder deposits in the mouth and throat, leaving little or no taste.

Low inhaler cost is ensured by many of the characteristics of the inhaler, including the absence of carrier, the use of standard capsules, and the small number of inhaler parts.

VII. CONCLUSION

Large porous powders possess a variety of potential advantages for pulmonary delivery of small and large molecules to the respiratory tract and systemic circulation. They can permit high-efficiency delivery with low-cost systems, and may broaden the field of inhaled therapies to include therapies that require sustained action and relatively high dose. Their commercial development at Alkermes continues to pose interesting formulation, testing, and manufacturing challenges and opportunities.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. D Edwards, J Hanes, G Caponetti, JS Hrkach, A Ben-Jebria, ML Eskew, J Mintzes, D Deaver, N Lotan, R Langer. Large porous aerosols for pulmonary drug delivery. Science 276:1868–1871, 1997.
2. L Adjei, J Garren. Pulmonary delivery of peptide drugs: effect of particle size on bioavailability of leuprolide acetate in healthy male volunteers. Pharm Res 7:565–569, 1990.
3. AR Clark, M Egan. Modelling the deposition of inhaled powder drug aerosols. J Aerosol Sci 25:175–186, 1994.
4. CN Davies, J Heyder, MC Subba Rumma. Breathing of half-micron aerosols. I. Experimental. J Appl Physiol 32:591–600, 1972.
5. I Gonda. Physicochemical principles in aerosol delivery. In: DJA Crommelin, KK Midha, eds. Topics in Pharmaceutical Sciences 1991. Stuttgart: Medpharm Scientific, 1992, pp. 95–115.
6. DA Edwards, A Ben-Jebria, R Langer. Recent advances in pulmonary drug delivery using large, porous inhaled particles. J Appl Physiol 85:379–385, 1998.
7. R Vanbever, JD Mintzes, J Wang, J Nice, D Chen, R Batycky, R Langer, DA Edwards. Formulation and physical characterization of large porous particles for inhalation. Pharm Res 16:1735–1742, 1999.
8. J Wang, A Ben-Jebria, DA Edwards. Inhalation of estradiol for sustained systemic delivery. J Aerosol Med 12:27–36, 1999.
9. A Ben-Jebria, D Chen, ML Eskew, R Vanbever, R Langer, DA Edwards. Large porous particles for sustained protection from carbachol-induced bronchoconstriction in guinea pigs. Pharm Res 16:555–561, 1999.
10. R Vanbever, A Ben-Jebria, JD Mintzes, R Langer, DA Edwards. Sustained release of insulin from insoluble inhaled particles. Drug Dev Res 48:178–185, 1999.
11. J Israelachvilli. Intermolecular and Surface Forces. 2nd ed. London: Academic Press, 1992.
12. Bot AI, Tarara TE, DJ Smith, SR Bot, CM Woods, JG Weers. Novel lipid-based hollow-porous microparticles as a platform for immunoglobulin delivery to the respiratory tract. Pharm Res 17:275–283, 2000.
13. RH Perry, DW Green. Perry's Chemical Engineers' Handbook. 6th ed. Section 20. New York: McGraw-Hill, 1984.
14. L Svarovsky. Solid-gas separation. In: JC Williams, T Allen, eds. Handbook of Powder Technology. New York: Elsevier, 1981, pp. 33–52.

Copyright © 2003 Marcel Dekker, Inc.

76

Dry Powder Inhalation Systems from Inhale Therapeutic Systems

Andy R. Clark
Inhale Therapeutic Systems, San Carlos, California, U.S.A.

I. INTRODUCTION

The inhaled route for the administration of protein and peptide therapeutics gives direct access to the lungs, where they are rapidly absorbed into the bloodstream through the large surface area (100 m^2) of the peripheral (deep) lung [1]. Advances in biotechnology are producing many new therapeutic biomolecules, but many are degraded within the gastrointestinal tract when administered orally. Inhaled formulations of new proteins and peptides offer an alternative to injections, thereby sparing patients the pain of needles and improving compliance. Moreover, small-molecule medications used to treat pain, seasickness, or migraine headaches, known to cause gastrointestinal upsets, may be replaced by inhalable medications.

II. UNIQUE REQUIREMENTS

However, successful delivery to the deep lung requires fine aerosol particles, 2–3 μm in diameter, to avoid impaction in the oropharyngeal cavity and ensure adequate deposition in the peripheral lung [2]. Therefore, medical inhalers for protein and peptide delivery are designed to maximize the generation of "fine" particles. In addition, an ideal medical inhaler should be reproducible, reliable, accurate, simple to use, durable, resistant to microbial contamination, and affordable, while at the same time keeping the drug chemically stable during storage and aerosolization [3].

Copyright © 2003 Marcel Dekker, Inc.

III. COMPARISON TO RELATED TECHNOLOGIES

The last 50 years have seen the evolution of three main types of inhalers: the nebulizer, which atomizes aqueous solutions; the pressurized metered-dose inhaler, which uses highly volatile propellant liquids; and dry powder inhalers (DPI), which deliver powdered drug formulations. In contrast to nebulizers and solution metered-dose inhalers, the formulation of dry powders used in DPIs is crucial to their performance [4]. The powdered drug must flow readily and not stick to the inhaler or packaging, yet generate a fine aerosol so that the patient can inhale a "respirable dose." In powder technology, this combination of factors can often be mutually exclusive. Fine powders usually clump and flow poorly, whereas coarser powders flow well, but generate few "respirable" particles. To combat this problem, coarse "carrier" particles are usually blended with fine drug particles to produce a powder that flows and generates a respirable aerosol in a DPI.

IV. INHALE'S PROPRIETARY TECHNOLOGY

To fulfill the requirements for a pulmonary protein product, scientists at Inhale Therapeutic Systems, Inc. developed dry powder formulations of soluble and insoluble peptides and proteins that are both highly dispersible, without the need for coarse carrier lactose particles, and stable at room temperature. These powders, coupled to a novel active inhaler device, deliver high drug doses per puff, and have low microbial control requirements during manufacture, i.e., bioburden versus sterility for liquid products. The dry powder formulation technology (PulmoSol™) is based on a proprietary glass stabilization technique, which dries proteins into an amorphous glass state that dramatically slows molecular interactions and hence inhibits denaturation of the molecules.

To produce the dry powders, highly customized powder processing equipment was developed. This equipment, which produces particles of 1–5 μm in diameter, is based on spray drying, but utilizes highly modified atomizers and collection techniques to maintain high manufacturing efficiency and hence commercial viability. However, the fine glass particles that are produced can rapidly absorb moisture from the air, which would plasticize the glass and destroy the protective nature of the amorphous state, with a consequent loss of shelf life. To prevent these problems, doses of the dry powders are individually packaged in foil blister packs that block moisture ingress. With unit packaging, different drug strengths can also be formulated. To fill the blister packs with fine powder, proprietary filling methods had to be developed to handle the minute particle sizes, and precisely control the small therapeutic doses. The SVE filling technology [5] has demonstrated the capability of filling doses as low as 1.5 mg with relative stan-

Copyright © 2003 Marcel Dekker, Inc.

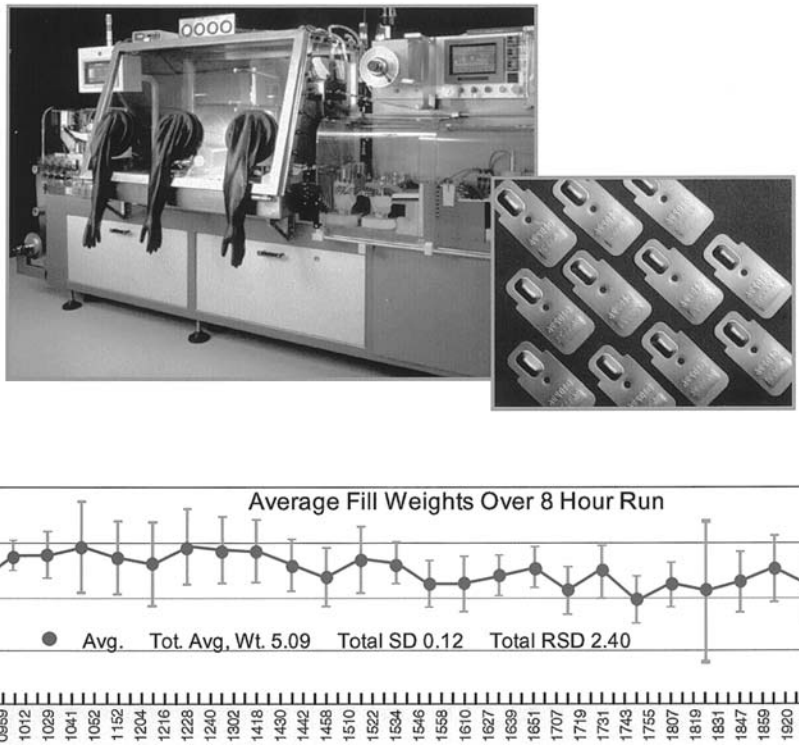


Figure 1 The PulmoSol blister filling equipment and dose reproducibility.

dard deviations of approximately 2–3% (Fig. 1). Although blister-filling technology is common throughout the pharmaceutical industry, no commercial technology is available to meet these special needs.

V. MECHANISM OF DRUG RELEASE

The blister pack slides easily and securely into a slot on the side of the specially designed inhaler. A component called a Transjector™ opens the blister and then utilizes a small compressed air bolus to entrain and aerosolize the powder. The device suspends and captures the fine aerosol powder in a small volume of air, known as a "standing cloud," which is then inhaled by the patient (Fig. 2). Unlike passive DPIs, Inhale's active device delivers an aerosol cloud with characteristics that are independent of the force of the patient's inhalation. The simple, durable

Copyright © 2003 Marcel Dekker, Inc.

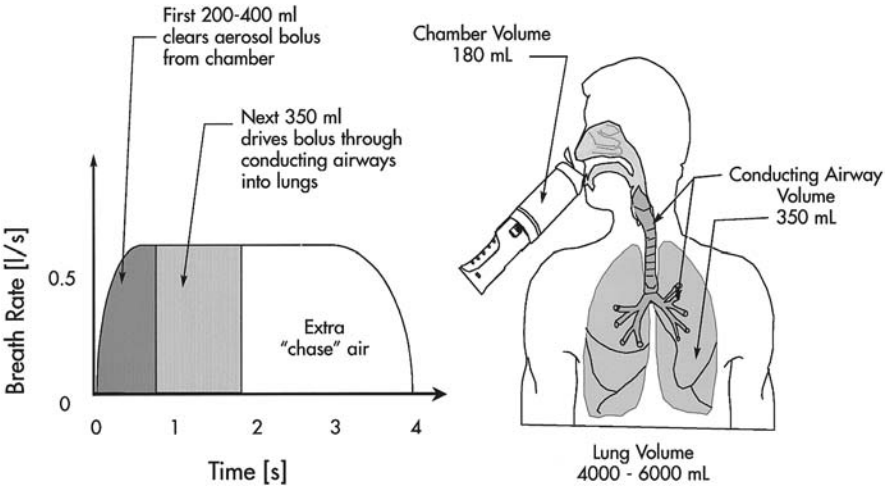


Figure 2 Theory of "standing cloud" peripheral aerosol delivery using the Inhale pulmonary delivery system.

device uses no batteries, electronics, or microchips, making it inexpensive to manufacture and extremely easy to maintain. The device has undergone a number of revisions during development. The original "proof of concept" prototype device was fairly large, but successive planned modifications during development [6] (Fig. 3) have condensed it to the size of a small flashlight (Fig. 4).

To obtain a dose of dry-powder medication, a patient places a unit dose blister pack into the side slot, closes a pneumatic handle (to store compressed air), and presses a button to release the compressed air. The standing cloud of aerosolized drug is visible in a clear chamber, and the patient opens the chamber mouthpiece and slowly inhales the drug. The chamber holds about 200 mL of air containing the medication, which an average person can easily inhale. Considering that a normal adult's tidal breath is about 700 mL and an average person's deep inhalation is 2–4 L, even patients with limited lung capacities should obtain consistent results (see Fig. 2).

VI. RESEARCH AND DEVELOPMENT

As early as 1925, it was demonstrated that insulin could be absorbed from the lung following aerosol delivery, although the bioavailability was only 3% and delivery was cumbersome [7]. More recently, numerous studies in humans and

Copyright © 2003 Marcel Dekker, Inc.

Figure 3 Prototype development sequence of the Inhale pulmonary delivery system from "proof of concept" to phase II device.

animal species have shown that many proteins and peptides, including leuprolide acetate, human growth hormone, parathyroid hormone, calcitonin, and interferon, are absorbed from the deep lung [8–14]. In general, biomolecules with lower molecule weights achieve higher absorption than high-molecular-weight biomolecules [15]. Absorption ranges from 20% to 50% for proteins for molecular weights less than 30 kDa [16], and many therapeutic biomolecules fall in this size range. For human insulin, absorption is faster following inhalation than by subcutaneous injection [17].

VII. SAFETY CONCERNS

To date, inhalation exposure has been well tolerated by patients. In numerous clinical studies lasting 6 months to a year or more, there have been no observa-

Copyright © 2003 Marcel Dekker, Inc.

Figure 4 The Inhale pulmonary delivery system.

tions of adverse lung reactions, anaphylaxis, or immune reactions [16]. In theory, fewer immunological reactions may occur with inhaled drugs than subcutaneous injections because the lung is continuously exposed to nonsterile materials in air. Direct measurement found lower levels of antibodies to human growth hormone following inhalation compared to subcutaneous injection in rats [18]. The lungs are robust, and appear capable of exposure to the few milligrams of a therapeutic protein that would need to be inhaled. For comparison, the lungs are exposed to about 4 mg of foreign material in a smoky bar, and about 50 mg/day of low-toxicity nuisance dust in many occupational settings [19].

Copyright © 2003 Marcel Dekker, Inc.

VIII. CLINICAL TRIALS

Pulmonary delivery of insulin is being explored by Pfizer Inc. and Aventis Pharma, who are testing an inhalable insulin product from Inhale Therapeutic Systems, Inc. (San Carlos, CA) [20–22]. Inhale's proprietary platform for insulin is now undergoing phase III clinical trials in partnership with Pfizer Inc. and Aventis Pharma. It is in early clinical development with Aventis Behring for the delivery of α,-antitrypsin proteinase inhibitor, with Enzon for the delivery of leuprolide and with Chiron for the delivery of tobramycin.

IX. SCALE-UP CHALLENGES

The quantity of dry powder and inhaler devices required obviously increases as clinical programs progress. Whereas research and development and phase I trials require milligram amounts of a drug, phase III clinical trials and commercialization may call for hundreds of kilograms of drug. In 1993, PulmoSol dry powder formulations were produced in batches of 10–100 mg in a Buchi benchtop spray dryer, equivalent to approximately 10 g/year. By 1995, demand for batches rose and batch size was increased to 250 g manufactured in a Niro Pilot Scale reactor. Today's phase III clinical trials materials and future large-scale commercial production is at the 5 kg/batch level. The Niro Large Scale reactor capable of manufacture at this scale stands three stories tall and has required advances in both atomizer and collection technologies to maintain consistent high-performance powder.

Device manufacture over this period has scaled accordingly. Prototype II, the device designed specifically for phase II clinical trials, was manufactured in soft tools and hand-assembled by Inhale, whereas commercial inhalers are being manufactured by two Original Equipment Manufacturer (OEM) suppliers.

X. REGULATORY ISSUES

The U.S. Food and Drug Administration (FDA) considers most protein inhalation therapeutics "combination products." Receiving regulatory approval involves an interplay of expertise in biologics, human drugs, and medical devices. The FDA's Division of Pulmonary Drug Products requires 1-year safety data on 200 patients, or 1 year in 100 patients and 6 months in 300 patients. Safety issues concern patient experiences with cleaning, durability, and failures of the DPI devices. The devices tested must be the same as the intended commercial devices and robust enough to withstand regular use by patients for the recommended time of

Copyright © 2003 Marcel Dekker, Inc.

use. In Europe, protein inhalation products are regulated as either a drug and device, or as a combination product. Obtaining a CE designation, which certifies that the product conforms to the relevant European Union directives relating to safety, will help the product move freely within the European Union without further national controls. The Inhale device has been CE-marked.

XI. FUTURE DEVELOPMENTS

Having developed PulmoSol technology, which produces stable, low-density, highly dispersible powders, Inhale has been working on second-generation technologies. These include new formulation platforms such as Pulmosphere™, a lipid-based particle engineering technology, and a new delivery device called Solo™, which uses the existing or new formulation technologies, and combines them with foil-foil blister packaging and a purpose-designed patient interface that allows the patient's inspiratory effort to facilitate aerosol generation and efficient, reproducible lung delivery (Fig. 5).

Figure 5 The Inhale Solo device.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. WM Thurlock. The internal surface area of nonemphysematous lungs. Am Rev Respir Dis 95:765–770, 1967.
2. W Stahlhofen, J Gebhart, J Heyder. Experimental determination of the regional deposition of aerosol particles in the respiratory tract. Am Ind Hyg Assoc J 41:385–398, 1980.
3. RK Wolff, RW Niven. Generation of aerosol drugs. J Aerosol Med 7:89–106, 1994.
4. Kassem, NM. Generation of deeply inspirable clouds from dry powder mixtures. PhD thesis, King's College, University of London, London, 1990.
5. MJ Rocchio, DE Wightmam, K Naydo, DJ Parks, AE Smith. Powder filling systems, apparatus and methods. US patent 5,826,633, 1998.
6. JD Burr, JM Anthony, GS Axford, JW Etter, AE Smith. Apparatus and methods for dispensing dry powder medicaments. US patent 6,089,228, 2000.
7. M Gansslen. Uber inhalation von insulin. Wien Klin Wochenschr 4:71–81, 1925.
8. JS Patton. Deep-lung delivery of therapeutic proteins. Chemtechnology 27:34–38, 1997.
9. PR Byron, JS Patton. Drug delivery via the respiratory tract. J Aerosol Med 7:49–75, 1994.
10. A Adjei, J Garren. Pulmonary delivery of peptide drugs: effect of particle size on bioavailability of leuprolide acetate in healthy male volunteers. Pharmacol Res 7: 565–569, 1990.
11. RB Elliott, BW Edgar, CC Pilcher, C Quested, J McMaster. Parenteral absorption of insulin from the lung in diabetic children. Aust Paediatr J 23:293–297, 1987.
12. LJ Deftos, BL Seely, PC Clopton. Intrapulmonary delivery of bone-active peptides: bioactivity of inhaled salmon calcitonin approximates that of injected calcitonin. Proc Am Soc Bone Min Res Annual Meeting, Seattle, 1996.
13. RS Pillari, BL Hughes, RK Wolff, JA Heisserman. The effect of pulmonary delivered insulin on blood glucose levels using two nebulizer systems. J Aerosol Med 9:227–239, 1996.
14. P Colthorpe, SJ Farri, IJ Smith, D Wyatt, G Taylor. The influence of regional deposition on the pharmacokinetics of pulmonary delivered growth hormone in rabbits. Pharm Res 12:356–359, 1995.
15. RH Hastings, M Grady, T Sakuma, MA Matthay. Clearance of different sized proteins from the alveolar space in humans and rabbits. J Appl Physiol 73:1310–1316, 1992.
16. RK Wolff. Safety of inhaled proteins for therapeutic use. J Aerosol Med 11:197–219, 1998.
17. BL Laube, A Georgopoulos, GKI Adams. Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. JAMA 269:2106–2109.
18. JS Patton, RM Platz. Pulmonary delivery of peptides and proteins for systemic action. Adv Drug Del Rev 8:179–196, 1992.
19. American Conference of Governmental Industrial Hygienists. Threshold limit values for chemical substances and physical agents and biological exposure indices. ACGIH, Cincinnati, 2:33, 1995.

Copyright © 2003 Marcel Dekker, Inc.

20. WT Cefalu, RA Gelfand, I Kourides, for the Inhaled Insulin Phase II Study Group. Treatment of type 2 diabetes mellitus with inhaled human insulin: a 3-month, multicenter trial. Diabetes 47(suppl 1):A61, 1998 (abstract 237).
21. WT Cefalu, CC Balagtas, WH Landschulz, RA Gelfand. Sustained efficacy and pulmonary safety of inhaled insulin during 2-years of outpatient therapy. Diabetes 49(suppl 1):A101, 2000 (abstract 406-P).
22. JS Skyler, RA Gelfand, IA Kourides, for the Inhaled Insulin Phase II Study Group. Treatment of type 1 diabetes mellitus with inhaled human insulin: a 3-month, multicenter trial. Diabetes 47(suppl 1):A61, 1998 (abstract 236).

Copyright © 2003 Marcel Dekker, Inc.

77
Spiros Inhaler Technology

Clyde Witham and Elaine Phillips
Elan Pharmaceutical Technologies, San Diego, California, U.S.A.

I. INTRODUCTION

Dura Pharmaceuticals has developed a small handheld, breath-actuated, battery-operated powder inhaler (Spiros®). The inhaler has an impeller that is actuated, when the patient inhales, to disperse and deliver the powder aerosol for inhalation. The breath actuation eliminates the patient coordination problems typically seen with pressurized metered-dose inhalers. The absence of propellants, such as the internationally restricted chlorofluorocarbons used in many such metered-dose inhalers, makes the Spiros inhaler environmentally safe.

The Spiros technology differs from first-generation dry powder inhalers (DPIs) including the Spinhaler, Rotahaler, and Turbuhaler. These earlier DPIs (and most others in development) rely on the patient's inspiratory rate to disperse particles, leading to variable powder dispersion because of inter- and intrapatient variability in inspiratory effort.

The core technology was initially developed to overcome the patient coordination required for metered-dose inhalers and the inspiratory effort required for first-generation dry powder inhalers in treating asthma. Since then, the technology has been recognized to have applicability for both topical and systemic delivery of both small molecules and proteins and peptides. The Spiros system is not yet commercially available. The first product will be inhaled insulin in partnership with Eli Lilly and Co. Several asthma drugs were in development with Spiros, but owing to decreasing market economics, were abandoned in mid-2000.

Copyright © 2003 Marcel Dekker, Inc.

II. SPIROS TECHNOLOGY

All motorized Spiros powder inhaler platforms use the same core technology [1], described in Figure 1, to achieve powder dispersion that is relatively independent of inspiratory flow rate over a broad range. The high-speed rotating impeller provides mechanical energy to disperse the powder. The impeller and battery power enable the powder dispersion to be independent of the ability of the patient to inhale vigorously.

The core technology is housed in the blisterdisk inhaler (Fig. 2), which is being utilized by Eli Lilly and Company for the delivery of pulmonary insulin.

The Spiros DPI blisterdisk powder storage system (Fig. 3) is designed for potentially moisture-sensitive substances (e.g., some proteins, peptides, and live vaccines). The blisterdisk powder storage system contains 16 unit doses. Powder formulation is filled and then sealed into a foil blister that protects the powder from exposure to high humidity and ultraviolet light, and reduces the risk of contamination. Capabilities for filling range from small scale (200 powder storage systems/batch) to automated cassette and blister assembly machines. Both automated systems are capable of filling up to 120 blisterdisks/min. Filling for GMP purposes is conducted in class 100-10,000 environments.

The inhaler is designed to actuate the motor 1500 times at which point a microprocessor causes a light-emitting diode (LED) on the inhaler to flash red, indicating to the patient that he can use the contents of up to two more blisterdisks. At 1500 actuations, the LED is solid red and the motor will no longer activate

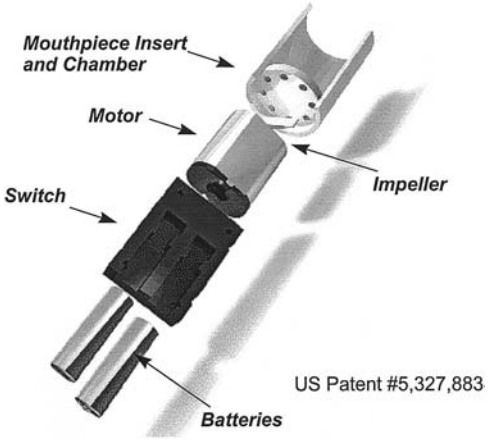


Figure 1 Aerosol generator "core" technology.

Copyright © 2003 Marcel Dekker, Inc.

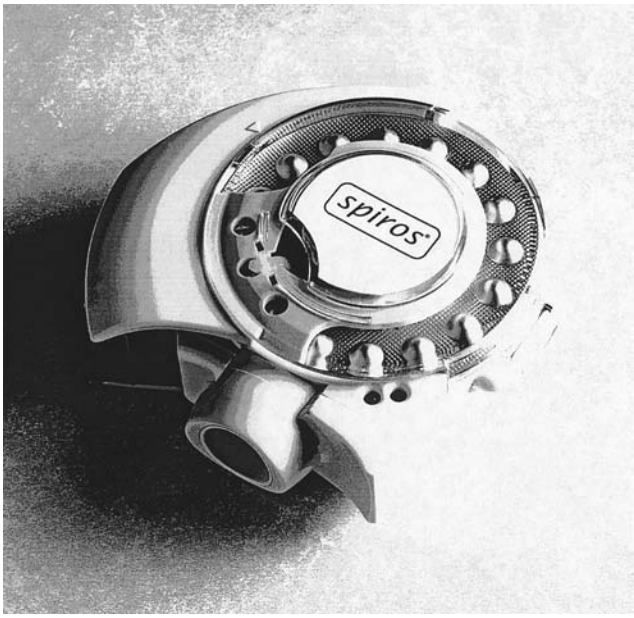


Figure 2 Spiros inhalation platform.

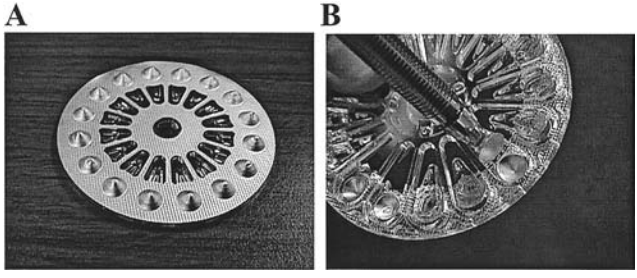


Figure 3 (A) Blisterdisk powder storage system. (B) The interior of a well in a blisterdisk.

Copyright © 2003 Marcel Dekker, Inc.

the impeller. This feature is designed to limit the lifetime of a given inhaler to a period of optimal performance.

A. Mechanism of Drug Delivery

Pulmonary drug delivery systems are intended for either topical or systemic delivery. To target the different regions of the lung, the formulation is designed such that the aerodynamic particle size distribution is controlled to a target size. Typically, to target the tracheobronchial regions of the lung to treat asthma, the aerodynamic size is targeted on the order of 5–10 μm. For systemic delivery, empirical models indicate that aerodynamic diameters on the order of 2–3 μm are preferred [2,3]. The aerodynamic particle size distribution is a function of the primary particle size of the material and the degree to which the material can be dispersed into discrete particles.

Once deposited, the solid particles dissolve and are absorbed. Typically, the plasma profiles for inhaled drugs have shorter times to maximum concentrations versus the subcutaneous and oral routes. Some investigation has been conducted to extend the release of drug from a solid matrix delivered to the lung. Here, however, consideration must be given to the potential involvement of the mucociliary escalator, alveolar macrophages, and various proteases. To extend the release of drugs, the active ingredient must first be incorporated into a matrix either physically, chemically, or both. The solid matrix must then be size-reduced to the target primary size. If the active ingredient is quite potent, then the size-reduced drug or drug matrix must be blended with a bulking agent, typically lactose, for accurate metering into the blisterdisk.

Formulations filled into the Spiros blisterdisk inhaler can consist of materials that have been formulated by any of the techniques shown in Figure 4. The most typical approach involves the active pharmaceutical ingredient being provided in a bulk crystalline or lyophilized form. The material is size-reduced by jet milling and, if necessary, blended with lactose prior to filling into the blisterdisk. Of the nominal dose filled into the blister well, a certain percentage is emitted from the inhaler. The emitted dose (ED) contains discrete drug particles of varying aerodynamic size. This aerodynamic particle size distribution is characterized in relationship to the target region of the lung.

B. Particle Size Reduction

A number of size reduction techniques are available including spray drying, precipitation from supercritical fluids, and jet milling. Jet milling differs from the other two techniques in that the active ingredient has been isolated in the solid state (e.g., by lyophilization) prior to the size reduction step [4]. Therefore, the

Copyright © 2003 Marcel Dekker, Inc.

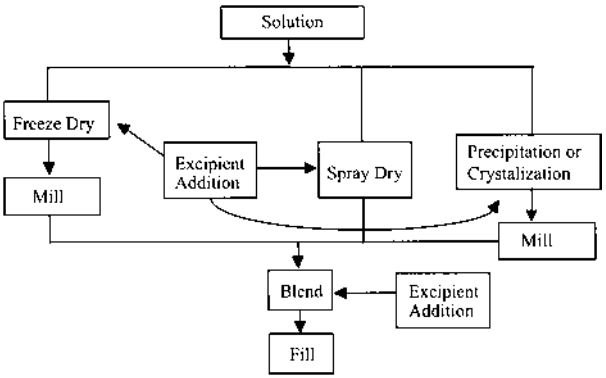


Figure 4 Preparation of dry powder formulation.

molecular mobility of the protein in the solid state is much reduced compared to that in the liquid state. This may help to protect the molecule during the size reduction step when high shear forces are used to isolate the particles. Dura's experience with jet milling indicates that milled proteins and peptides exhibit minimal to no detectable degradation or loss of activity [5].

A typical example of size distribution data obtained by jet milling a lyophilized peptide is shown in Figure 5. These data demonstrate that the size reduction process produces a narrow distribution, is reproducible, and generates particles in the target range for optimal pulmonary delivery. Dura has been very successful with milling as a size reduction technique. Bioactivity has been maintained in 95+% of the macromolecules evaluated to date. This includes a live attenuated vaccine.

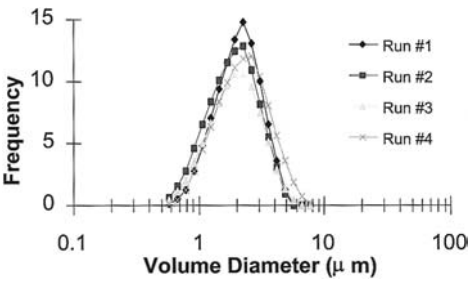


Figure 5 Size distribution of a peptide milled under the same conditions.

Copyright © 2003 Marcel Dekker, Inc.

C. Blending

Typical formulations for the Dura powder inhaler use 100M lactose as a carrier for the drug particles. The lactose particles are large (~100 μm) and they facilitate the handling and dispersion of the smaller drug particles. The total mass of each dose is usually on the order of 6–12 mg, of which some percentage is the active drug. In some instances, drug concentration may be as low as 2% and in other cases may be as high as 100%. The target blend concentration is determined from the desired systemic dose and the estimated efficiency of pulmonary delivery.

III. AEROSOL PERFORMANCE EVALUATION

A. Aerosol Performance Parameters

Two key measures of aerosol performance are assessed for a powder for inhalation. The first is the *emitted dose*, that is, the total quantity of active material that exits from the mouthpiece of the inhaler and is available for dosing to the patient. Figure 6 shows that emitted doses over consecutive shots are consistent using different inhalers.

The second aerosol performance parameter is the *respirable dose*, that is, the quantity of protein that is expected to deposit in the lungs based on particle size. Andersen cascade impactors (ACI) are used to determine the mass median aerodynamic diameter (MMAD) of particles dispersed from the inhaler. The *respirable fraction* (RF) is often defined as the percent of the emitted dose that is less than 5.8 μm MMAD. For systemic delivery of proteins and peptides the desired MMAD is in the range of 1–3 μm. Figure 7 shows ACI data for three model peptides and a protein that were milled and blended with lactose in concentrations ranging from 2 to 50%.

B. Stability/Activity Assessment

Proteins and peptides can be sensitive to preparation processes and may lose activity by aggregation (or other degradation routes). A goal of preformulation work is to stabilize the protein during processing and storage, at concentrations appropriate for attaining the final target dose. Physical and chemical stability is evaluated at several storage temperatures and relative humidities at various time points, consistent with ICH guidelines. Representative data demonstrating aerosol stability of a micronized peptide blended with lactose are shown in Figure 8.

Analytical methods that assess the chemical purity and strength of the drug, such as high-performance liquid chromatography, are generally transferred from the partner and implemented at Dura. Throughout formulation development, the activity of the protein is assessed using various in vitro/in vivo technologies.

Copyright © 2003 Marcel Dekker, Inc.

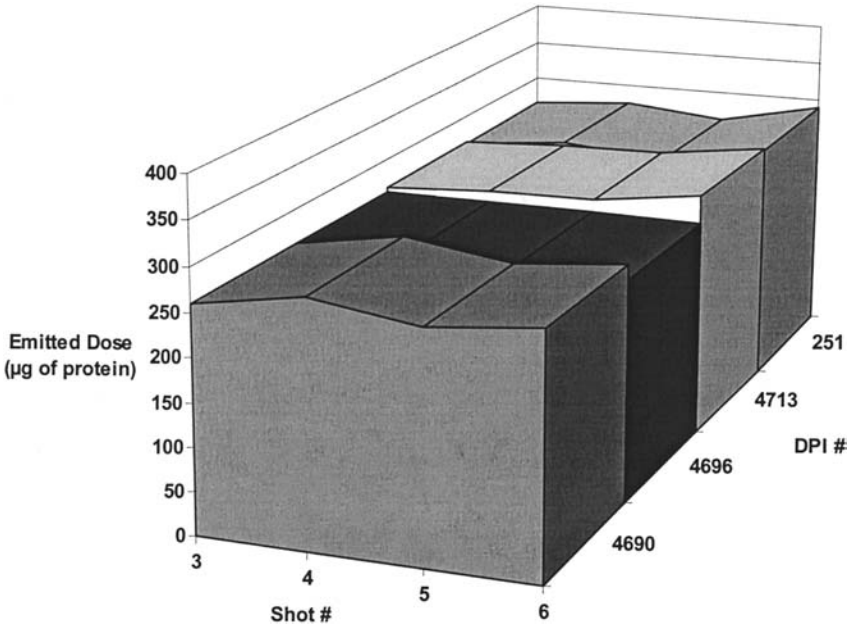


Figure 6 Consistency of emitted doses with different inhalers for a representative protein.

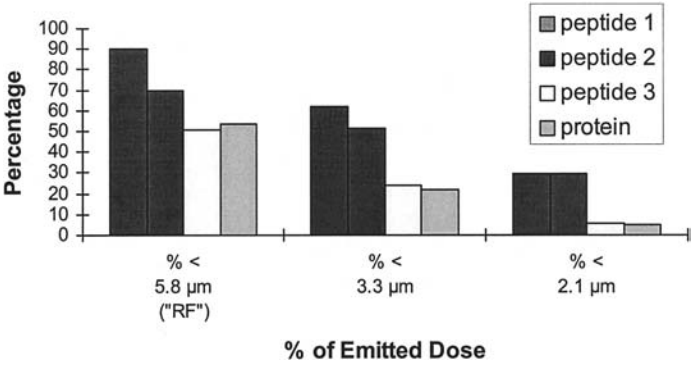


Figure 7 Aerosol performance of protein and peptide formulations with Spiros.

Copyright © 2003 Marcel Dekker, Inc.

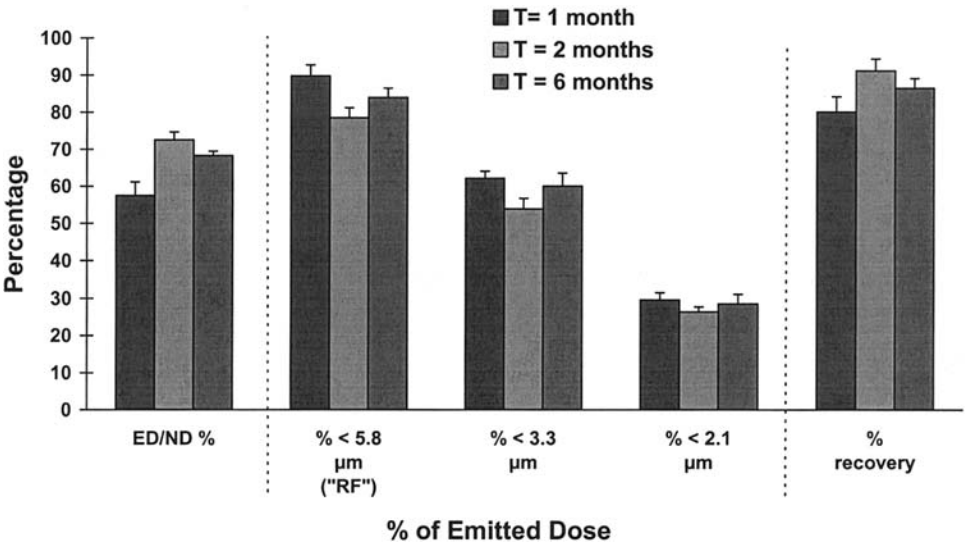


Figure 8 Aerosol stability of a micronized peptide blended with lactose.

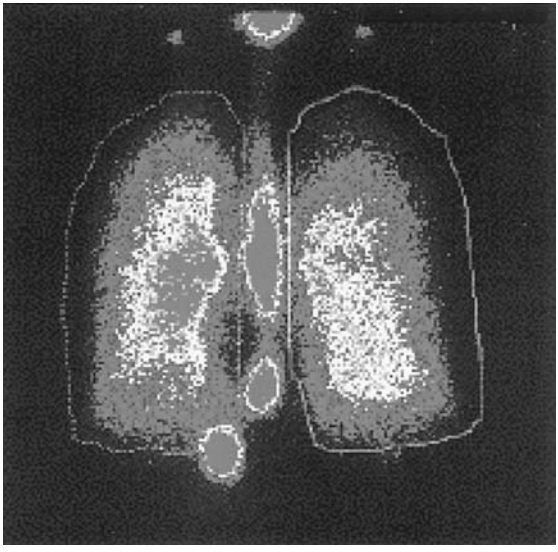


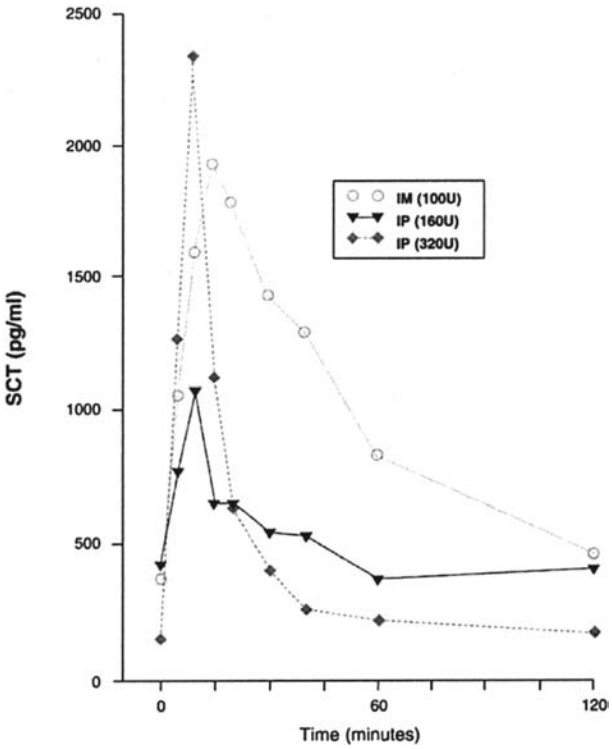
Figure 9 Pulmonary imaging with radiolabeled albuterol slow inspiration (15 L/min). (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

Dura develops additional physical and chemical tests to assess the performance of the formulation as needed.

IV. HUMAN CLINICAL STUDIES

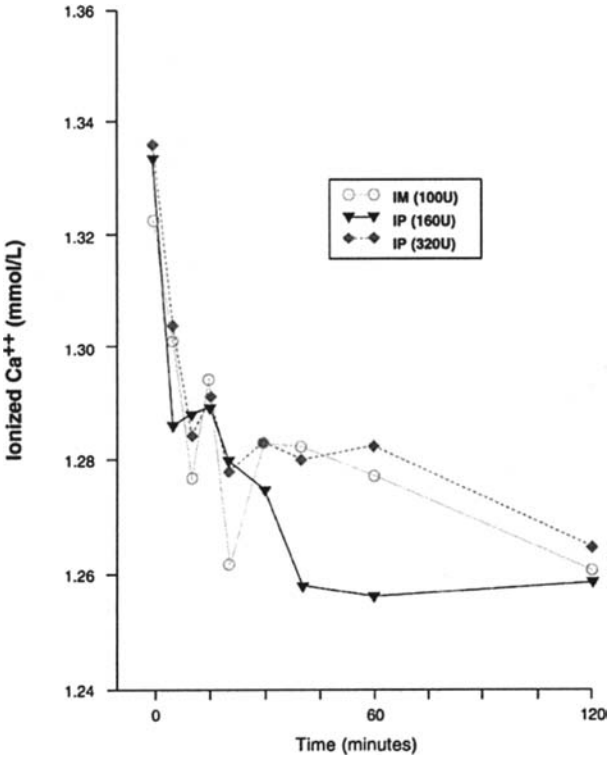
Clinical trials through phase III have been completed for two asthma drugs, albuterol sulfate and beclomethasone diproprionate. For these programs, over 500,000 clinical doses were given with the Spiros cassette inhaler. These formulations are intended to provide a topical dose to the lungs. Scintigraphy results show uniform deposition of radiolabeled albuterol throughout the tracheobronchial region and significant and uniform deposition in the alveolar region (Fig. 9) [6].



(A)

Figure 10 Bioavailability (A) and bioactivity (B) of inhaled salmon calcitonin for intrapulmonary (IP) versus intramuscular (IM) administration.

Copyright © 2003 Marcel Dekker, Inc.



(B)

Figure 10 Continued

To demonstrate the potential of Spiros with macromolecules in vivo, Dura provided clinical trial materials for a phase I study with salmon calcitonin (sCT), a polypeptide used to treat osteoporosis and other bone diseases. A stable dry powder formulation of sCT was produced under Good Manufacturing Practices (GMP) for the study. In a random crossover design, all 10 subjects received 100 IU of sCT (Miacalcin) by intramuscular injection, for comparison with pulmonary delivery of sCT. Five of the 10 subjects received 160 IU (1 puff) by inhalation, and the remaining five received 320 IU (2 puffs) by inhalation. Blood levels of sCT and biochemical markers, such as total serum calcium, were measured. The study indicated that sCT is absorbed from the lung (Fig. 10A), and is active systemically in lowering serum calcium (Fig. 10B). In addition, a single exposure to inhaled calcitonin appeared to be well tolerated.

Copyright © 2003 Marcel Dekker, Inc.

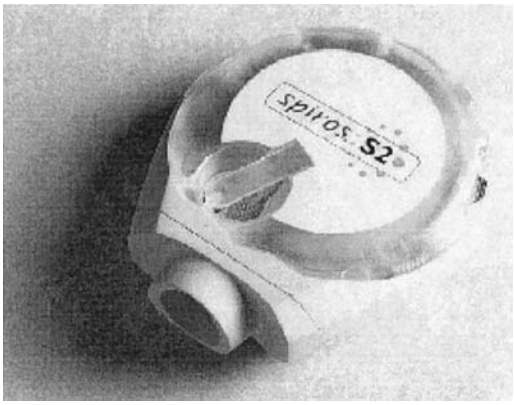


Figure 11 Multidose S2.

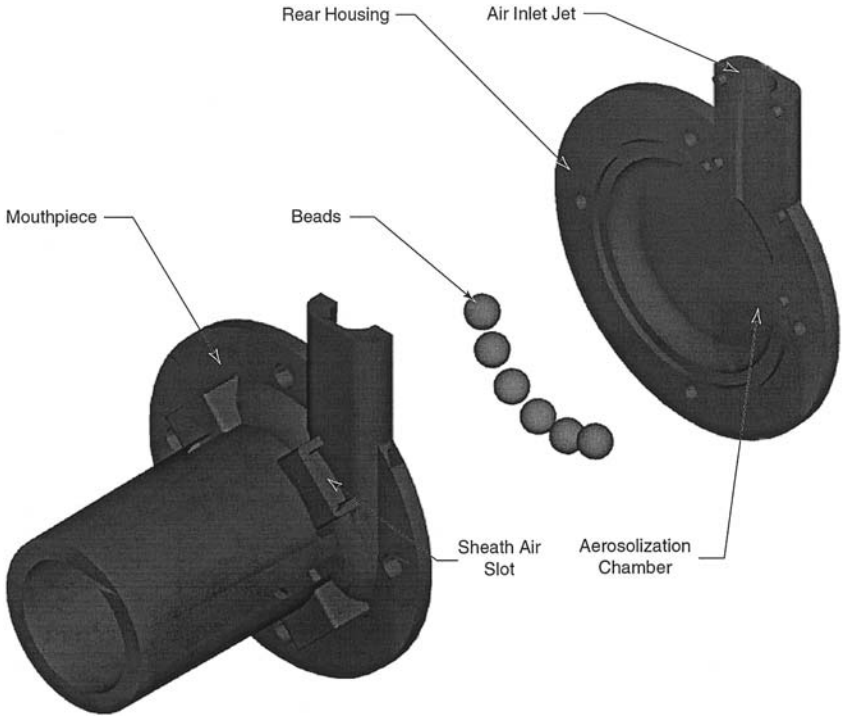


Figure 12 Unit-dose S2.

Copyright © 2003 Marcel Dekker, Inc.

V. NEXT-GENERATION TECHNOLOGY

The Spiros motorized system works well to overcome the dose-to-dose variability due to patient variance, but for low-cost drugs, the inhaler may be too expensive. Therefore, Dura embarked on a project to design and build an inhaler that retains the benefits of the motorized system (low flow, low effort, high efficiency) yet does not require a motor or batteries. The result of that effort is the Spiros S2 platform.

Spiros S2 is a *motorless* powder inhalation technology. Its simple design includes a unique powder dispersion mechanism incorporating free-floating beads and a dosing chamber configured to precisely control airflow characteristics (Figs. 11 and 12).

Spiros S2 is designed to achieve efficient aerosol performance with low inspiratory flow rates and minimal effort on behalf of the patient, and to deliver a wide range of drugs and dose strengths. In addition, by interfacing with Dura's replaceable blisterdisk powder drug storage system, this new design also leverages existing commercial manufacturing capabilities. The S2 technology is cost-effective, simple, easy to use, and is intended for development as both unit-dose and multidose drug applications.

REFERENCES

1. DR Williams, MB Mecikalski, DO Thueson. Apparatus for aerosolizing powdered medicine and process and using. US patent 5,327,883, 1994.
2. PR Byron. The prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J Pharm Sci 75:433–438, 1986.
3. L Adjei, J Garren. Pulmonary delivery of peptide drugs: effect of particle size on bioavailability of leuprolide acetate in healthy male volunteers. Pharm Res 7:565–569, 1990.
4. RM Platz, A Ip, CL Witham. Process for preparing micronized polypeptide drugs. US patent 5,354,562, 1994.
5. E Phillips, E Allsopp, T Christensen, M Fitzgerald, L Zhao. Size reduction of peptides and proteins by jet-milling. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Buffalo Grove, IL: Interpharm Press, 1998, pp. 161–168.
6. M Hill, L Vaughan, M Dolovich. Dose targeting for dry powder inhalers. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery V. Buffalo Grove, IL: Interpharm Press, 1996, pp. 197–208.

Copyright © 2003 Marcel Dekker, Inc.

78

The Respimat, a New Soft Mist Inhaler for Delivering Drugs to The Lungs

Bernd Zierenberg
Boehringer Ingelheim Pharma KG, Ingelheim, Germany

Joachim Eicher
Steag microParts, Dortmund, Germany

I. INTRODUCTION

The inhalation of drugs provides the most direct noninvasive route either for treating respiratory disorders topically or for administering drugs systematically. To ensure that the drug reaches the lungs, it must be administered as an aerosol. This means that the required amount of drug per application consists of drug particles, either solid or liquid droplets in a size range of 1–5 μm, which are inhaled by the patient. In the past, pressurized metered-dose inhalers (pMDIs) have been popular devices for generating inhalable aerosols. These devices depend on chemical propellants to generate an aerosol from a drug solution or suspension; however, their future is now uncertain.

Early pMDIs containing chlorofluorocarbon (CFC) propellants are currently being phased out, and there are also concerns over the global warming potential of alternative propellants such as hydrofluoroalkanes, developed to replace CFCs. Efforts to develop alternative devices include various dry powder inhalers but these have their own shortcomings, as described by Ganderton [1]. There is therefore an urgent need for a convenient propellant-free inhaler device to deliver aerosols from solutions.

This chapter describes the setup, development, and performance data of Respimat® (Boehringer Ingelheim, Ingelheim am Rhein, Germany), a novel soft

Copyright © 2003 Marcel Dekker, Inc.

mist inhaler, designed to substitute for pMDIs, to improve their existing performance, and to broaden the possibility of delivering drugs via the lungs.

II. GENERAL TECHNICAL APPROACHES FOR SOFT MIST INHALERS AND RESPIMAT

The generation of an inhalable aerosol from a drug solution requires that the bulk liquid be dosed and then converted into appropriately sized droplets. There are several technically feasible methods for achieving the aerosolization of a drug solution in a pocket-sized device. These methods (e.g., piezoelectric effect [2], extrusion through micron-sized holes [3], electrohydrodynamic effect [4]) require either electric energy from a battery or mechanical energy to produce the aerosol. In any case, the energy has to be focused in an intelligent way for the aerosolization process. This is necessary to ensure that the applied energy is transformed into droplet-generating energy in a sufficiently efficient manner. In the case of Respimat, the technical breakthrough is based on the approach of forcing drug solution through a two-channel nozzle [5]. During this process the solution is accelerated and split into two converging jets. By impaction of the jets, which converge at a carefully controlled angle, the drug solution disintegrates into inhalable droplets. This new patented procedure of aerosolizing a liquid requires only a small amount of mechanical energy, which is easily generated by the hand of the patient. Additionally, this approach has no need for a battery, which would increase costs and the need for maintenance by the patient.

III. DEVELOPMENT OF RESPIMAT

The concept was demonstrated in a laboratory model, consisting of a metal body with a syringe as a solution reservoir (Fig. 1), and was shown to function correctly. The device was operated by means of a lever arm, which simultaneously tightened the mainspring and withdrew a metered volume of drug solution of about 13.5 μL from the reservoir. Pressing a button released the spring, forcing the metered dose through the channels as liquid jets that impact 25 μm from the nozzle outlet to produce the aerosol. A feasibility study using an aqueous drug solution of a β_2-agonist showed that the droplet size distribution in the aerosol was in the range suitable for inhalation; the majority of the particle mass was in the size range 1–5 μm.

In this first model, the nozzle openings were tiny holes pierced into a stainless steel disk; however, a nozzle design better suited for mass production was needed. This was achieved by developing a miniature "sandwich" concept, the

Copyright © 2003 Marcel Dekker, Inc.

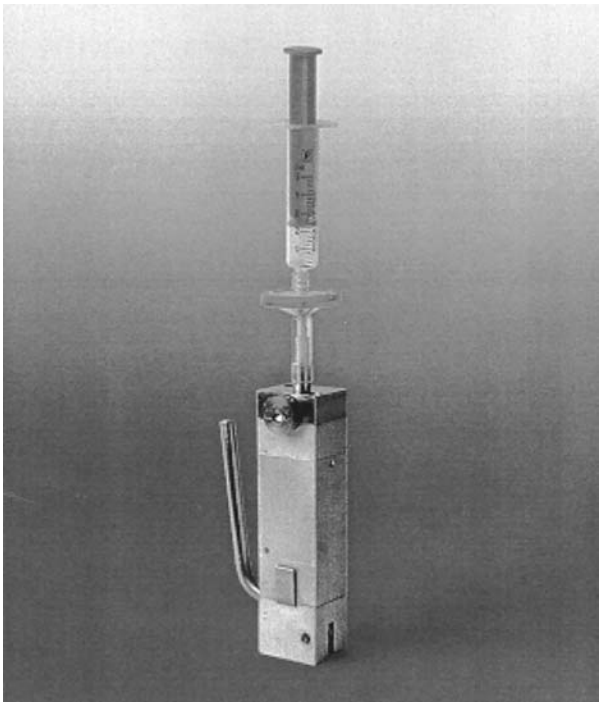


Figure 1 Laboratory model for demonstrating correct functioning of the concept. (See color insert.)

uniblock, consisting of a rectangle (2 × 2.5 mm) cut from a glass plate bonded to a silicon wafer. By use of photolithographic techniques adapted from the microelectronics industry, multiple copies of the uniblock, each comprising filter structures as well as inlet and outlet channels (Fig. 2), are etched into the silicon wafer with high precision and accuracy. Currently, the accuracy of the photolithographic exposure process is better than 0.1 μm over a single uniblock bearing the etched nozzle microstructure.

Further development of this first model included exchanging all metal parts for components made from polymers whenever possible and adapting all parts of the device for mass production. In addition, the torque required for loading the dose was minimized (approximately 40 cNm) so that the energy needed to generate the aerosol could be easily produced by hand. After initial stability and technical performance tests, the device was successfully used in the first lung deposition study, in comparison with a pMDI containing CFCs, carried out on healthy volunteers.

Copyright © 2003 Marcel Dekker, Inc.

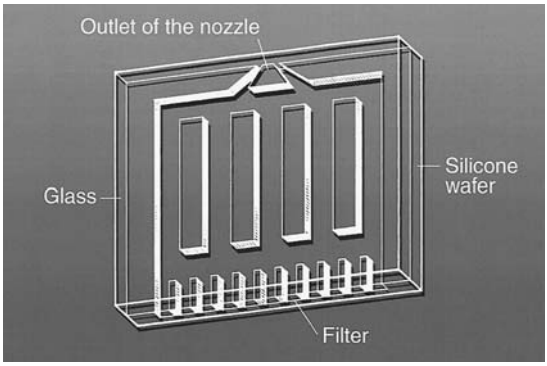


Figure 2 Schematic drawing of the uniblock. (From Ref. [5].) (See color insert.)

The experience accumulated with the various prototypes (I–IV) and the need to make a functional practical device with a smaller number of individual components were combined with the results of device-handling studies, in which patients evaluated the four different design concepts. The resultant device, Prototype IV, incorporated a radical change in design. Compared to the prototype I design, which released the dose at an angle of 90° relative to the device exit (i.e., the mouthpiece was at right angles to the drug cartridge), the final design released the dose in a direction parallel to the exit. This parallel version (Fig. 3) is currently being tested in clinical phase II and phase III studies.

Figure 3 Prototype IV of Respimat used in clinical trials. (From Ref. [5].) (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

IV. MODE OF ACTION OF RESPIMAT

The principal parts of Respimat are shown in a schematic diagram (Fig. 4). To use the device, the patient removes the bottom case, inserts the cartridge containing the drug solution, and replaces the case. The cartridge is now connected by a capillary tube (containing a nonreturn valve) to the uniblock. To load a dose, the patient simply turns the lower half of the device through 180°. The helical can transforms the rotation into a linear movement, which tightens the spring and moves the capillary with the nonreturn valve to a defined lower position. During this movement, the drug solution is drawn through the capillary into a pump chamber as shown in Figure 4. When the patient presses the release button to actuate the device, the mechanical power from the spring pushes the capillary with the now closed nonreturn valve to the upper position. This operation drives the metered volume of drug solution (about 13.5 μL) through the nozzle in the

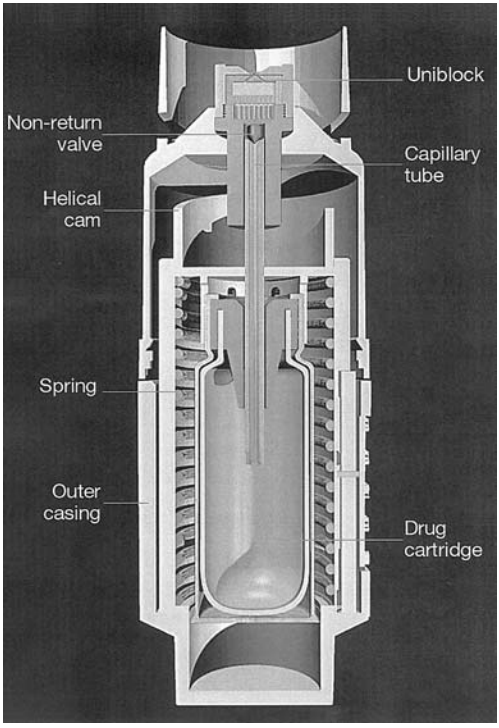


Figure 4 Schematic drawing of the key elements of Respimat. (From Ref. [5].) (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

uniblock. Here the two fine jets of liquid are produced at the outlet of the uniblock, which converge at a carefully controlled angle. The resulting impact of the two jets of liquid generates a slow-moving aerosol cloud, or soft mist. When a cartridge is inserted for the first time, the device has to be primed to expel air from its inner parts. The device is then ready for use.

V. RESPIMAT PERFORMANCE DATA

A. Technical Performance Data

Respimat is an active system, which means that the aerosol is generated by a constantly available and consistent energy source and that its quality in terms of dose and particle size distribution is independent of both the patient's inspiratory flow and ambient conditions. Water, ethanol, or a mixture of both can be used as a solvent for formulating the drug solution. Aqueous drug solutions also contain the two excipients benzalkonium chloride and EDTA as preservatives.

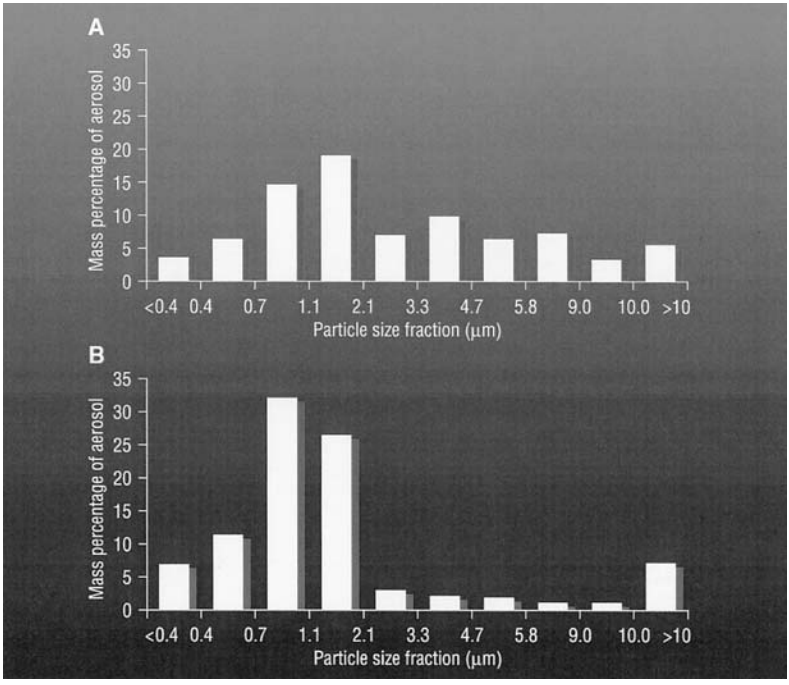


Figure 5 Particle size distribution for aerosols generated by Respimat using (A) aqueous drug solution (β_2-agonist) and (B) ethanolic solution (steroid). (From Ref. [5].) (See color insert.)

Copyright © 2003 Marcel Dekker, Inc.

The fine-particle fraction, defined as the mass percentage of the aerosol consisting of particles smaller than 5.8 μm, is higher for an ethanolic formulation than for an aqueous formulation generated by the Respimat. Figure 5 shows typical examples of the particle size distribution of aqueous and ethanolic solutions measured in an Anderson Cascade Impactor (Anderson Instruments, Inc., Smyrna, GA). The fine-particle fraction amounts to approximately 66% for the aqueous drug solution (β_2-agonist) and 81% for the ethanolic drug solution (corticosteroid). These values are 2.5 times higher than the corresponding values for aerosols produced by chlorofluorocarbon pMDIs. This particle size distribution can also be described in terms of a mass median aerodynamic diameter value. The mass median aerodynamic diameter values with Respimat were 2.0 ± 0.4 μm for the aqueous solution and 1.0 ± 0.3 μm for the ethanolic solution, both of which were determined by measurements with an Anderson Cascade Impactor conducted at a temperature of 22°C ± 2°C and a relative humidity of 50 ± 10%.

The velocity of the aerosol output generates a relatively long duration of dose release by Respimat (approximately 1.2 and 1.6 s for aqueous and ethanolic solutions, respectively), which should facilitate maximal inhalation of the dose, allowing the patient time to inhale after pressing the dose-release button, in contrast to the critical need to coordinate actuation and inspiration that is required during the use of pMDIs. In addition, the soft mist produces a perceptible taste or sensation, providing appropriate feedback to indicate that the dose has been released in contrast to findings with some powder inhalers.

B. Clinical Performance Data

The in vitro performance data of the aerosol produced by Respimat led to the hypothesis that the delivery of drugs to the lungs is improved compared to the existing treatment with pMDIs. This hypothesis was tested in several scintigraphic deposition studies carried out in volunteers and patients. In these studies the radionuclide ^{99m}Tc is added to the formulation so that it forms a physical association with the micronized drug particles in a suspension formulation (e.g., of a pMDI) or is incorporated into the droplets of a solution formulation. The topographical deposition of the aerosol in the lungs is visualized using a gamma camera and quantified in terms of the percentage of lung or oropharyngeal deposition with reference to the metered dose. A survey of the numerical results obtained for pMDIs, dry powder inhalers, and Respimat with this type of investigation is reported by Newman [6]. In summary, the deposition data show that the soft mist generated by Respimat, both from an aqueous solution with the drug fenoterol and from an ethanolic solution with the drug flunisolide, results in a two- to threefold increase in lung deposition compared to the corresponding pMDI. In parallel, the oropharyngeal deposition is significantly reduced for the aerosol administered by Respimat.

Copyright © 2003 Marcel Dekker, Inc.

Finally, the ratio of deposition in peripheral regions to deposition in the central lung zone is similar for Respimat and a pMDI. The increased drug delivery to the lungs from Respimat measured with the gamma scintigraphy technique suggests that clinically comparable therapeutic responses should be achievable with lower doses administered to patients from Respimat compared to a pMDI.

In two clinical studies for aqueous drug solutions with fenoterol (Berotec®) and the combination of fenoterol/ipratropium bromide (Berodual®), this expected result was confirmed. For Berotec, 12.5 and 25 μg administered by Respimat were therapeutically equivalent to either 100 or 200 μg administered via pMDI [7]. For Berodual, the bronchodilatory effects of 25/10 or 50/20 μg (fenoterol/ipratropium bromide) doses administered via Respimat were equal or slightly superior to the recommended dose of 100/40 μg given via pMDI [8]. These results suggest that the improved lung deposition observed with Respimat allows lower absolute doses to be administered for a similar clinical effect in the local treatment of lung diseases. Additionally Respimat's high performance may result in a more efficient systemic delivery of drugs via the lungs.

VI. CONCLUSIONS

Demonstrating a new approach to inhalation therapy, Respimat, a propellant-free inhaler with a novel patented mechanism of generating a soft mist from a dosed volume of a drug solution, shows distinct advantages over contemporary inhaler devices. Like many other inhalers Respimat delivers multiple doses of an aerosol; however, Respimat does this actively without the use of propellants. Respimat simply uses mechanical energy that is easily produced by the patient before each administration. The soft mist demonstrates improved particle characteristics compared to existing inhalers, especially chlorofluorcarbon pMDIs, thereby increasing the targeting of drugs to the lungs. The particle size distribution of the aerosol generated by Respimat is practically influenced only by the surface tension and the viscosity of the drug solution. At ambient conditions these parameters do not change much; therefore, Respimat produces the soft mist in a repeatable and consistent manner regardless of the ambient temperature ($T = 15–30°C$), pressure, or humidity.

In response to the needs of patients highlighted in handling studies, refinements to the device will be incorporated, and the resultant first-market version of Respimat is designed to meet widespread patient acceptance coupled with physician approval of the improved therapeutic targeting. Besides the local treatment of lung diseases, the systemic administration of drugs with the lungs as the point of entry will become more important. This is mainly driven by the upcoming development of drugs with a protein structure. For this type of drug, the inhalative route could be a convenient and safe method of delivery into the body.

Copyright © 2003 Marcel Dekker, Inc.

REFERENCES

1. D Ganderton. Targeted delivery of inhaled drugs: current challenges and future goals. J Aerosol Med 12:3–8, 1999.
2. LR De Young, I Chambers, S Narayan, C Wa. The Aerodose Multidose Inhaler device design and delivery characteristics. In: RN Dalby, PR Byron, SJ Farr, eds. Respiratory Drug Delivery VI. Buffalo Grove, IL: Interpharm Press, 1998, pp. 91–95.
3. J Schuster, R Rubsmen, P Lloyd, J Loyd. The AERx aerosol delivery system. Pharm Res 14:354–357, 1997.
4. WC Zimlich, JY Ding, DR Busick, RR Montvic, ME Placke, PH Hirst, GR Pitcarn, S Malik, SP Newman, F Macintyre, PR Miller, MT Shepherd, TM Lukas. The development of a novel electrohydrodynamic pulmonary drug delivery device. In: RN Dalby, PR Byron, SJ Farr, J Peart, eds. Respiratory Drug Delivery VII. Raleigh, NC: Seratec Press, 2000, pp. 241–246.
5. B Zierenberg. Optimizing the in vitro performance of Respimat. J Aerosol Med 12: 19–24, 1999.
6. SP Newman. Use of gamma scintigraphy to evaluate the performance of new inhalers. J Aerosol Med 12:25–31, 1999.
7. FV Measen, JA van Noord, JJ Smeets, APM Greefhorst. Dose range finding study comparing a new soft mist inhaler with a conventional metered dose inhaler (MDI) to deliver fenoterol in patients with asthma. Eur Respir J 10:1281, 1997.
8. J Goldberg, E Freund, B Jahnel, R Hinzmann. Combination fenoterol/ipratropium bromide delivered via a new soft mist inhaler: dose range finding study in patients with asthma in comparison with a conventional metered dose inhaler (MDI). Am J Respir Crit Care Med 157:801, 1998.

Copyright © 2003 Marcel Dekker, Inc.

79

Regulatory Issues for Pulmonary Delivery Systems

Darlene Rosario and Babatunde Otulana
Aradigm Corporation, Hayward, California, U.S.A.

I. INTRODUCTION

Advancements in pulmonary drug delivery technology for the delivery of both small and large molecules (e.g., protein and peptides) have resulted in a proportional increase in the regulatory requirements for the registration of new inhalation drug products. The regulatory concerns are primarily in response to the unknown effects of delivering specific molecules to the lungs over time and the desire to control these new products to performance standards at least comparable to the standards for currently marketed pulmonary products, i.e., metered-dose inhalers (MDIs) and dry powder inhalers (DPIs). The industry together with professional societies is working with regulatory agencies on the requirements for the approval of new inhalation drug products. For example, an industry group, International Pharmaceutical Aerosols Consortium—Regulatory Science (IPAC-RS), and the professional society American Association for Pharmaceutical Science (AAPS) are working with regulatory authorities to advance consensus-based and scientifically driven standards and regulations for inhaled and intranasal products. At present, the available guidance on specific aspects of drug development, including chemistry, manufacturing, and controls (CMC), toxicology, and clinical development, from health authorities, is based on the existing inhalation products such as MDIs and DPIs and, in some cases, limited number of approved new inhalation drug products.

Traditionally, pulmonary drug delivery products such as MDIs and DPIs are regulated in the United States as drug-device combinations in accordance

Copyright © 2003 Marcel Dekker, Inc.

with the Food and Drug Administration (FDA) Inter-Agency Agreement of 1991 [1]. Newer products with sophisticated drug delivery devices, for example, the AeroDose Delivery Device (AeroGen Inc., Sunnyvale, CA), the AERx System (Aradigm Corporation, Hayward, CA), and the Inhance Drug Delivery Device (Inhale Therapeutics, San Carlos, CA), have raised the question as to the appropriateness and possibility of a separate authorization or 510K notification of the delivery device via FDA's Center for Devices and Radiological Health (CDRH). However, many companies developing these new delivery systems for marketing in the United States have proceeded via the drug-device combination approach, filing investigational new drug applications with the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) and proceeding down the path of product registration as a combination drug product rather than seeking a separate device application such as a premarket authorization (PMA) or a 510K clearance. This approval path is in contrast to the requirements for these products outside the United States.

The dichotomy between drug and device approvals also exists in the regulatory environment and approval path for pulmonary drug delivery products in the European Union (EU). In the EU, the device is "approved" in accordance with the medical devices directive (93/42/EEC), including the requirement for a CE marking of conformity, at marketing, from a notified body licensed by a competent authority such as the British Medical Device Agency. Depending on the regulatory approval path chosen for marketing authorization, centralized or decentralized (mutual recognition) procedure, the marketing application would be approved by national authorization or the European Medicines Evaluation Agency (EMEA).

Regardless of the registration path for the marketing (licensing) application for these newer, sophisticated pulmonary drug delivery products, some common issues must be addressed to satisfy compendial and regulatory requirements for approval. These common issues include unique chemistry, manufacturing and controls, animal toxicology testing, and, finally, the challenges of conducting clinical trials with a dosage form where dosimetry is often difficult to calibrate.

II. CHEMISTRY, MANUFACTURING, AND CONTROLS

In the United States and EU, one particular issue has dominated the compendial and regulatory discussions in the last few years: the development of appropriate in vitro tests that result in meaningful specifications to assess and control the quality and safety of the inhaled product. Specifically, industry and regulatory authorities have struggled with establishing appropriate standards for testing and acceptable specifications for emitted dose uniformity of the aerosol and particle size distribution of the emitted dose. Regulatory agencies are recommending that the tests and accompanying specifications are established using clinical batches,

Copyright © 2003 Marcel Dekker, Inc.

biobatch, primary stability, and production batches to appropriately define and control the characteristics of the product.

In the United States, the FDA has issued two draft guidance documents for industry outlining the specifications, and in some instances the acceptance criteria, for MDIs, DPIs, nasal spray and inhalation solutions, suspension and spray drug products [2,3]. These draft guidances address the formulation components, including the active ingredient(s), the method of manufacturing and packaging, specifications for the drug product, container and closure systems, and drug product stability. The MDIs and DPIs draft guidance argues that these products are "complex units for which the quality and reproducibility can be better ensured by appropriate controls of all components (active ingredients, excipients, device components and packaging) used in the manufacture, controls during manufacture of the drug product, and controls of the drug product." For nasal sprays and inhalation solutions, suspension and spray drug products, the draft guidance argues, "the potential wide array of inhalation spray drug product designs with unique characteristics will present a variety of development challenges." To this end, the guidances recommend data on each drug product component, the quantitative composition of the formulation, appropriate controls for the formulation components (both active ingredients and excipients), as well as the method of manufacturing and packaging. For drug product specifications, the FDA requires a complete description of the release acceptance criteria, analytical methods, and sampling plans that ensure the identity, strength, quality, purity, and performance of the drug product through its shelf life and in-use conditions. Test methods for these criteria are to be documented in sufficient detail to permit duplication and verification by FDA laboratories and include validation with respect to accuracy, sensitivity, specificity, reproducibility, and ruggedness. Specific test parameters (e.g., volume of air passing through the device during the test for emitted dose) are recommended for both MDIs and DPIs [2] as well for inhalation solutions [3]. In some cases the draft guidance recommends acceptance criteria, which are believed to assure batch-to-batch control, with respect to the formulation, manufacturing process, and function of critical drug delivery components (e.g., the valve of an MDI). For example, the draft guidance recommends an acceptance criterion for emitted dose content uniformity as two-tier testing with prescribed limits. For particle size distribution, specific methodology (multistage cascade impactor) and testing requirements are recommended that include aerodynamic particle size distribution analysis with prescribed limits in addition to reporting of mass balance.

In the EU, the Committee for Proprietary Medicinal Products (CPMP) issued a guidance [4] that became effective December 1998 for the development of DPIs. Although DPI systems have been marketed in the EU for a number of years, the development of DPIs has increased as an alternative to chlorofluorocarbon-free MDIs. The CPMP guidance addresses similar topics to the FDA's guidances. The CPMP guidance addresses the composition of DPIs, including

Copyright © 2003 Marcel Dekker, Inc.

dose uniformity, airflow resistance, aerodynamic size assessment of fine particles, the formulation, through-life performance, method of preparation, and the control of starting materials. The CPMP guidance recommends control tests on the finished product, and rather than prescribe limits, it recommends presentation of data.

In addition to the FDA draft guidance for nasal spray and inhalation solutions, suspension and spray drug products, an additional CMC requirement was published as a final rule in May 2000 for oral inhalation solutions. The FDA issued a final rule requiring aqueous-based drug solutions for oral inhalation to be manufactured sterile [5]. The FDA has concluded that current manufacturing methods and safeguards against microbial contamination, including microbial limits, have not been sufficient to prevent microbial contamination of nonsterile aqueous-based drug products for oral inhalation. The final rule became effective May 27, 2002.

III. PRECLINICAL TOXICOLOGY TESTING

Although the general preclinical toxicology requirements for topical pulmonary drugs such as those for asthma and chronic obstructive pulmonary disease (COPD) are well understood by manufacturers of these products, there is little guidance in the public domain from regulatory authorities specific to toxicological testing of aerosol products. Not surprisingly therefore, there is no published guideline for toxicology testing of systemic drug delivered via the lungs using the newer, more sophisticated pulmonary delivery systems. The assumption in industry is that the requirements for these products would be similar to those for asthma and COPD products.

For chronically administered inhalation drug products, regulatory agencies have usually imposed similar requirements as for other products, e.g., solid oral dosage forms, except that the toxicology program must include delivery to test animals by inhalation. Intravenous administration may be used to achieve toxicologically relevant systemic concentrations when there are difficulties with bioavailability via the lung or by the oral route.

The toxicology studies are expected to assess both topical and systemic toxicities of the product and should include both genders of at least two species of animals (a rodent and a nonrodent), and be conducted in accordance with good laboratory practices. The duration of exposure expected is usually similar to that of other drug products and ranges from 14-day studies to 12-month exposure in relevant animal species. In general, to support human trials, regulatory authorities expect to see preclinical animal studies of at least the same duration as the clinical trials. Pharmacokinetic and toxicokinetic studies are also used to assess levels of systemic exposure and correlation with observed toxicities as well as to guide dose escalation in clinical trials.

Copyright © 2003 Marcel Dekker, Inc.

In addition to the standard toxicological safety testing, inhalation products are often required to undergo special animal testing such as hypersensivity tests, reproductive tests, genotoxicity, and carcinogenicity tests, depending on the type of drug product and the extent of existing database on its preclinical and clinical safety. These studies are usually conducted in line with existing guidelines, which have been issued by both the FDA and the CPMP and are broadly applicable to most pharmaceuticals and biotechnology products. The International Conference on Harmonization (ICH) also has issued a number of general guidelines on carcinogenicity (S1A, S1B, S1C); genotoxicity (S2A, S2B), reprotoxicity (S5A, S5BM), in addition to standard preclinical toxicology requirements (S3A, S3B, S4A, S6). While there are few guidelines specific to inhalation products, the FDA published a paper on considerations for toxicological testing of respiratory products that summarizes reviewers' expectation on these tests [6].

There are a number of challenges for toxicological testing of inhalation products in animals. The technical difficulties of administering aerosols to animals have been aptly reviewed in some publications and texts [7,8]. For breath-actuated delivery systems, a different delivery device, e.g., a nebulizer, must be used to generate the aerosol into the animal dosing chamber. This raises the issue of direct toxicological testing of extractables from the device components and the container closure system. As a result, separate testing of extractables from the container closure and leachables in the formulation is required in such instances, and based on the identity of the compounds and levels, may require animal toxicology testing.

The FDA requirements for extractable and leachable testing in inhalation products is described in the draft guidances for MDI and DPI products [2] and for nasal spray and inhalation solution, suspension and spray drug products [3]. In summary, the agency requires that the identity and concentration of leachables in the drug formulation be determined through the end of the drug product's shelf life and, where possible, correlated with the extractable profiles of the container closure components determined under various control extraction study conditions. These extractable and leachable tests are usually conducted using compendial tests described in USP 87 and 88. Additional testing of extactables/leachables, including animal toxicology testing, may be required depending on the nature of the extracted materials and residues.

IV. CLINICAL REQUIREMENTS

There is a dearth of specific guidance for the design and conduct of clinical testing of aerosol products from regulatory agencies around the world. The sole exception has been in the area of bioequivalence testing of generic inhalation products, where both the FDA [9] and the CPMP have published broad testing

Copyright © 2003 Marcel Dekker, Inc.

and approval requirements. Although the FDA issued "points to consider" for clinical development programs for MDI and DPI Drug Products in September 1994 [10], the requirements outlined in the guidance pertain mostly to asthma and COPD indications. In general, sponsors have had to apply guidance requirements issued for various disease indications, where they exist, to design clinical programs with inhalation products. Thus, a sponsor developing an inhalation product for diabetes should pay careful attention to FDA's requirement for development of products for the treatment of diabetes, which describes study design, choice of end-points, and acceptable criteria for safety and efficacy.

The ICH has issued a number of guidelines on safety (S7) and efficacy (E1A–E9) of clinical trials including general considerations for clinical trials (E8) and good clinical practice (E6).

In addition to meeting various regulatory requirements for efficacy and safety for the specific disease indications, clinical testing of the newer pulmonary devices also poses some new challenges. These delivery systems are generally more complex and more sophisticated than existing MDIs and DPIs. This raises two issues: ease of use and acceptability of the device, and its robustness and reliability under various conditions of use. The first issue is usually addressed by training to ensure patients comply with the instructions for use. In addition, some devices have built-in functions that facilitate ease of use; e.g., the AERx system from Aradigm Corporation [11] has dosing lights that guide patients to inhale at the appropriate inspiratory flow rate and volume. As for the robustness of the delivery system, regulatory agencies are requiring sponsors to incorporate device end-points in their clinical trials to establish the system reliability under conditions of intended use.

Changes to the critical components of the delivery system, to address usability or reliability, should be implemented during the phase I and phase II stages of clinical testing. Finally, and notwithstanding the therapeutic areas for which the delivery system is intended, it is essential that the pivotal trials be conducted with the final configuration of the system, which is the same as the to-be-marketed product. No changes should be made to the product once phase III testing is begun, except high-volume manufacturing scale-up in preparation for commercial production. With the increasing sophistication and complexity of the newer pulmonary delivery systems, it is likely that the impact of such changes would be more difficult to quantify without extensive in vitro or in vivo testing, and regulatory authorities are more likely to require expensive and time-consuming clinical validation of such late-stage modifications.

V. CONCLUSION

Regulatory guidance from health authorities for the development of new pulmonary delivery systems is limited. Manufacturers have only a handful of published

Copyright © 2003 Marcel Dekker, Inc.

draft guidances specific to inhalation products from which to help guide the development of these products. However, regulatory agencies around the world have demonstrated openness and increasing willingness to provide one-on-one interaction and guidance for individual sponsors. In addition, a number of guidelines and regulations from the FDA, CPMP, and ICH, which apply broadly to pharmaceutical and biotechnology products, provide further guidance for development of pulmonary drug delivery products. Close attention to these available resources, routine communication with regulatory agencies with data-driven alternatives, and well-designed clinical studies are critical to successful development and ultimate approval of these new sophisticated pulmonary delivery systems.

REFERENCES

1. Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health, October 1991.
2. Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry, Manufacturing, and Controls Documentation, October 1998.
3. Guidance for Industry. Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation, May 1999.
4. Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Dry Powder Inhalers, December 1998.
5. Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation. Final Rule. Federal Register, Volume 65, Number 103, May 26, 2000.
6. JJ DeGeorge. Considerations for toxicology studies of respiratory drug products. Regul Toxicol Pharmacol 25:189–193, 1997.
7. RK Wolff, MA Dorato. Toxicologic testing of inhaled pharmaceutical aerosols. Crit Rev Toxicol 23:343–369, 1993.
8. RF Phalen. Methods in Inhalation Toxicology New York: CRC Press, 1997.
9. Interim Guidance for Documentation of In Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers), January 1994.
10. Points to Consider. Clinical Development Programs for MDI and DPI Products, September 1994.
11. JA Schuster. The AERx aerosol delivery system. Pharm Res 14:354–357, 1997.

Copyright © 2003 Marcel Dekker, Inc.

80

Regulatory Issues Relating to Modified-Release Drug Formulations

Patrick J. Marroum
Food and Drug Administration, Rockville, Maryland, U.S.A.

I. INTRODUCTION

In recent years the use of modified-release (MR) drug formulations has increased considerably. This is partly due to advances in formulation technologies enabling one to design formulations that provide a better control of the release of the drug to the site of action. Controlled-release formulations provide several advantages over conventional immediate-release (IR) formulations of the same drug, such as a reduced dosing frequency, a decreased incidence and/or intensity of side effects, a greater selectivity of pharmacological activity, and a reduction in drug plasma fluctuation resulting in a more constant or prolonged therapeutic effect.

However, MR formulations provide unique challenges from a formulation and manufacturing point of view requiring specific studies to characterize the controlled-release nature of the formulation. In this chapter the regulatory considerations that come into play in approving and maintaining such formulations on the market will be discussed with an emphasis on the laws, regulations, and guidances that pertain to this type of drug delivery formulation.

The requirements discussed in this chapter cover all types of controlled-release dosage forms. The primary focus will be on oral controlled-release drug products, which are the most common type of controlled-release dosage form. Requirements for other types of controlled-release drug products, such as transdermal patches or implants, are similar to those described in this chapter.

Copyright © 2003 Marcel Dekker, Inc.

II. DEFINITIONS

Before beginning a discussion of the regulatory requirements of controlled-release products it is useful to understand several commonly used definitions for these types of products:

Controlled-release dosage forms: A class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower-than-normal manner [1].

Modified-release dosage form: Refers, in general, to a dosage form for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms [1].

Extended-release dosage form: This is a specific type of MR dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate (conventional)-release dosage form (IR) [1].

Delayed-release dosage form: This is a specific type of MR dosage form that releases a drug at a time other than promptly after administration. An example is enteric-coated tablets [1].

Proportional similarity:

Definition 1: All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients exactly half that of a tablet of 100-mg strength and twice that of a tablet of 25-mg strength) [2].

Definition 2: The total weight of the dosage form remains nearly the same for all strengths (within 5% of the total weight of the strength on which a biostudy was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredient and one or more of the inactive ingredients. For example, with respect to an approved 5-mg tablet, the total weight of new 1- and 2.5-mg tablets remains nearly the same, and the changes in the amount of active ingredient are offset by a change in one or more inactive ingredients. This definition is generally applicable to high-potency drug substances where the amount of active drug substance in the dosage form is relatively low [2].

III. CONTROLLED-RELEASE NEW DRUG APPLICATIONS

A fundamental question in evaluating a controlled-release product is whether formal clinical studies of the dosage form's safety and efficacy are needed or whether only a pharmacokinetic evaluation will provide adequate evidence for approval. A rational answer to this question must be based on evaluation of the pharmacokinetic properties and plasma concentration/effect relationship of the

Copyright © 2003 Marcel Dekker, Inc.

drug. Where there is a well-defined predictive relationship between the plasma concentrations of the drug and the clinical response (regarding both safety and efficacy), it may be possible to rely on plasma concentration data alone as a basis for the approval of the controlled-release product. In the following situations, it is expected that clinical safety and efficacy data be submitted for the approval of the controlled-release new drug application (NDA):

- When the controlled-release product involves a drug that is an unapproved new molecular entity, since there is no approved reference product to which a bioequivalence claim could be made.
- When the rate of input has an effect on the drug's efficacy and toxicity profile.
- When a claim of therapeutic advantage is intended for the controlled-release product.
- When there are safety concerns with regard to irreversible toxicity.
- Where there are uncertainties concerning the relationship between plasma concentration and therapeutic and adverse effects or in the absence of a well-defined relationship between plasma concentrations and either therapeutic or adverse clinical response.
- Where there is evidence of functional (i.e., pharmacodynamic) tolerance.
- Where peak-to-trough differences of the IR form are very large.

In all the above instances where there is already an IR formulation of the drug, a 505(b)(2) NDA could be submitted for approval to the Food and Drug Administration (FDA). The regulations for a 505(b)(2) NDA are covered under 21CFR 314.54. These regulations state that any person seeking approval of a drug product that represents a modification of a listed drug, for example, a new indication or a new dosage form, and for which investigations other than bioavailability or bioequivalence studies are essential to the approval of the changes, may submit a 505(b)(2) application. However, such an application may not be submitted under this section of the regulations for a drug product whose only difference from the reference listed drug is that the extent of absorption or rate of absorption is less than that of the reference listed drug or if the rate of absorption is unintentionally less than that of the reference listed drug [3].

IV. CODE OF FEDERAL REGULATIONS: BIOAVAILABILITY STUDY REQUIREMENTS FOR CONTROLLED-RELEASE PRODUCTS

The bioavailability requirements for controlled-release products are covered in the U.S. Code of Federal Regulations under 21 CFR 320.25(f)[4].

Copyright © 2003 Marcel Dekker, Inc.

The aims of these requirements are to determine that the following conditions are met:

The drug product meets the controlled-release claims made for it.
The bioavailability profile established for the drug product rules out the occurrence of clinically significant dose dumping. This is usually achieved by the conduct of a food effect study whereby the drug is administered with and without a high-fat breakfast.
The drug product's steady-state performance is equivalent to a currently marketed noncontrolled-release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

The reference material for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled-release claims made for the drug product. The reference material is normally one of the following:

A solution or suspension of the active drug ingredient or therapeutic moiety.
A currently marketed IR drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of the IR drug product.
A currently marketed controlled-release drug product subject to an approved full NDA containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling proposed for the controlled-release drug product.

Guidelines for the evaluation of controlled-release pharmaceutical dosage forms provide assistance to those designing, conducting, and evaluating studies. However, a drug may possess inherent properties that require considerations specific to that drug and its dosage form that may override the generalities of these guidelines. Guidances related to the evaluation of controlled-release drug products as well as many other types of guidances are available on the Internet, at the Center for Drug Evaluation and Research Web site (*http://www.fda.gov/cder/*).

V. GENERAL APPROACHES FOR EVALUATING CONTROLLED-RELEASE PRODUCTS

A. Demonstration of Safety and Efficacy Primarily Based on Clinical Trials

In general, for drugs where the exposure-response relationship has not been established or is unknown, applications for changing the formulation from IR to MR

Copyright © 2003 Marcel Dekker, Inc.

will require demonstration of the safety and efficacy of the product in the target patient population. Typically the approval of such applications will be based on the results of the pivotal clinical trials (at least two trials that are deemed pivotal to the assessment of the drug product from a clinical point of view).

In these cases, the pharmacokinetic and biopharmaceutics studies conducted are for descriptive purposes [5] and in certain cases will help in the initial dose selection. The types of pharmacokinetic studies generally include:

Single-dose relative bioavailability.
Multiple-dose relative bioavailability.
Food effect study.
Single-dose bioequivalence (BE) studies (clinical versus market formulations, different dosage strengths, etc.).
Dosage strength proportionality.
Dose proportionality study.
In vivo–in vitro correlation (IVIVC).
Pharmacokinetic-pharmacodynamic (PK/PD) evaluation.

When a new molecular entity is developed as a MR dosage form, additional studies to characterize its clinical pharmacology and absorption, distribution, metabolism, and excretion (ADME) characteristics are recommended.

1. Example of an NDA with Clinical Data

The NDA for the once-a-day formulation of diltiazem represents a typical example of an application with clinical data. The clinical portion of the NDA consisted of three clinical trials. The first trial was a randomized, double-blind placebo run in parallel-group pilot study with 36 patients with mild to moderate hypertension (24 on diltiazem 360 mg and 12 on placebo). The purpose of the trial was to investigate the time-effect relationship of the diltiazem formulation. The second trial was considered to be one of the two pivotal trials and was a dose-response trial in patients with mild to moderate hypertension. This was a multicenter, randomized, double-blind, placebo-controlled, fixed-dose response trial investigating 90, 180, 360, and 540 mg once-a-day diltiazem and placebo. A total of 229 patients participated in the study, which consisted of a 4-week run-in phase followed by a 4-week active treatment period. The third trial (the second pivotal trial) was a multicenter dose titration trial for the treatment of mild to moderate hypertension. The trial was a multicenter, randomized, double-blind, placebo-controlled parallel study comparing optimally titrated doses ranging from 120 to 360 mg of diltiazem to placebo in a total of 117 patients [6].

The biopharmaceutics and clinical pharmacology portion of the NDA consisted of four studies:

Copyright © 2003 Marcel Dekker, Inc.

A single-dose, relative bioavailability study comparing the controlled-release formulation to the approved IR formulation.
A pivotal steady-state relative bioavailability and dose proportionality study.
A food effect and absorption profile study.

The sponsor also conducted a pilot relative bioavailability study to select the formulation with optimal release characteristics and also used the data obtained from this study to develop a multiple Level C IVIVC [7].

The approval was mainly based on the results of the safety and efficacy trials where the biopharmaceutics studies were undertaken to characterize the release properties of the formulation and ensure that no dose dumping is occurring.

B. Demonstration of Safety and Efficacy Based on PK, PK/PD Trials

The "Guidance for Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" states:

> Sometimes clinical efficacy of modified-release dosage formulations can be extrapolated from existing studies, without the need for additional well-controlled clinical trials because other types of data allow the application of known effectiveness to the new dosage form. Even in the cases where blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that the new dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial [8].

The types of studies and requirement will depend on the nature of the exposure-response relationship and whether the therapeutic window is defined, as outlined below.

1. There Is No Prior Knowledge of the Exposure-Response Relationship or Therapeutic Window; Approval Is Solely Based on Plasma Concentrations

Such an approach, although being used in developing an MR product, is not encouraged. In such a case strict bioequivalence between the IR and MR product is required in terms of C_{max}, C_{min}, and AUC at steady state.

The impact of differences in the shapes of the plasma concentration-time profile for the IR and MR products should be assessed depending on the knowledge of the drug, the therapeutic class, and the proposed indication for the drug.

Copyright © 2003 Marcel Dekker, Inc.

In certain instances, an MR product may be developed to actually mimic the performance of an IR product and its dosing regimen (e.g., Repetabs). The MR product is designed to simulate actual multiple single-dose administrations that would correspond to individual dosage administrations of the IR product. Under such circumstances, with or without PK/PD information, it is conceivable that approval of the MR product could be based strictly on bioequivalence determinations for the PK parameters. When deviations in the steady-state PK profiles are seen between the MR and IR product regimens, more dependence on PK/PD information or clinical studies would be required for approval rather than on simple bioequivalence of the pharmacokinetic parameters of AUC, C_{max}, and C_{min}.

2. There Is No Quantitative Exposure-Response Relationship but a Well-Defined Therapeutic Window in Terms of Safety and Efficacy

In the case where the rate of input is known not to influence the safety and efficacy profile, the following criteria have to be met for the approval of such a product:

- The 90% confidence interval for the log-transformed ratio of the AUC_{ss} of the controlled-release formulation relative to the IR-approved formulation should be between 80 and 125 (where ss = steady state).
- The $C_{max,ss}$ should be equal to or below the upper limit of the defined therapeutic window.
- The $C_{min,ss}$ should be equal to or above the lower limit of the defined therapeutic window.

In the case where the rate of input is known to influence the safety and efficacy profile or is unknown, the approval criteria are the same as above. In addition, studies investigating the impact of the rate of input on the pharmacodynamics of the drug in terms of safety and efficacy should be investigated.

3. There Is a Well-Defined Quantitative Exposure-Response Relationship Shown Using Different Input Rates of IR or the MR Product

Under such circumstances, where adequate efficacy and safety PK/PD relationships exist, further safety and efficacy studies may not be required. The exposure-response relationship should be established with the intended clinical end-point. The safety profile of the drug should be well understood. In such situations, steady-state comparative bioavailability/bioequivalence (BA/BE) study(s) would be required to demonstrate that the MR product performs in a manner that ensures safety and efficacy under the labeled dosing conditions. In addition, the standard PK/BA studies would also be required for descriptive and labeling purposes.

Copyright © 2003 Marcel Dekker, Inc.

Under circumstances where clinical responses or surrogates of such responses related to efficacy or safety have been preliminarily related to PK parameters or dose, further safety or efficacy studies may be required to confirm the preliminary PK/PD relationships. It is anticipated that such additional safety or efficacy studies would not be of the same scale where no preliminary PK/PD relationships had been shown. The standard PK/BA studies would also be required for descriptive and labeling purposes in such situations.

If the exposure-response relationship is established with a validated surrogate end-point, the surrogate end-point used should be accepted as a validated marker for clinical efficacy. In addition, the safety profile of the drug should be well understood.

VI. GENERAL CONSIDERATIONS IN EVALUATING PK/PD RELATIONSHIPS FOR CONTROLLED-RELEASE DRUG PRODUCTS

In assessing PK/PD relationships for controlled-release products, it is important not only to establish concentration-effect relationships, but also to determine the significance of differences in the shape of the steady-state concentration versus time profile for an MR product regimen as compared to the approved IR product regimen. In this regard, any differential effects based on the rate of absorption and/or the fluctuation within a profile as related to safety and/or efficacy should be determined. Issues of tolerance to therapeutic effects and toxic effects related to drug exposure, concentration, absorption rate, and fluctuation should also be examined as part of the PK/PD assessment.

In certain cases minimizing fluctuation in a steady-state profile for an MR product may be desirable to reduce toxicity, while maintaining efficacy as compared to the IR product regimen (i.e., theophylline products). In other cases, minimizing fluctuation in a steady-state profile for an MR product may reduce efficacy (i.e., nitroglycerin fosters tolerance) as compared to the IR product regimen's profile where higher fluctuation is observed. It is therefore important and necessary to know or study the profile shape versus PD relationships. Commonly made assumptions regarding therapeutic superiority or equivalency through fluctuation minimization in an MR product regimen versus an IR product regimen must be verified.

VII. GENERIC EQUIVALENCE OF AN APPROVED CONTROLLED-RELEASE PRODUCT

The Drug Price Competition and Patent Term Restoration Act amendments, of 1984, to the Food, Drug, and Cosmetic Act gave the FDA statutory authority to

Copyright © 2003 Marcel Dekker, Inc.

accept, and approve for marketing, abbreviated new drug applications (ANDAs) for generic substitutes of pioneer products, including those approved after 1962. To gain approval according to the law, ANDAs for a generic controlled-release drug product must, among other things, be both pharmaceutically equivalent and bioequivalent to the innovator controlled-release product, which is termed the reference listed drug product as identified in FDA's Approved Drug Products with Therapeutic Equivalence Ratings (the Orange Book).

A. Pharmaceutical Equivalence

As defined in the Orange Book, to be pharmaceutically equivalent, the generic and pioneer formulations must (a) contain the same active ingredient; (b) contain the same strength of the active ingredient in the same dosage form; (c) be intended for the same route of administration; and (d) be labeled for the same conditions of use. The FDA does not require that the generic and reference listed controlled-release products contain the same excipients, or that the mechanism by which the release of the active drug substance from the formulation be the same [9]. For substitution purposes the two products have to be pharmaceutical equivalents.

B. Bioequivalence Requirements

The same BE requirements apply to the establishment of the equivalence of the formulation used in efficacy trials if it is different from the formulation intended for marketing and generic controlled-release product approval. For MR products submitted as ANDAs, the following studies are recommended [2]:

1. A single-dose replicate fasting study comparing the highest strength of the test and reference listed drug product.
2. A food effect nonreplicate study comparing the highest strength of the test and reference product. A typical meal consists of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash brown potatoes, 8 oz of whole milk [10]. Alternatively, other meals with 1000-calorie content, with 50% of the calories derived from fat, could be used. The dosage form should be administered immediately following the completion of the breakfast or meal.

Since single-dose studies are considered more sensitive in addressing the primary question of BE [11] (release of the drug at the same rate to the same extent), multiple doses are no longer more recommended even in instances where nonlinear kinetics are present [12]. This is departing from the long-standing policy that was outlined in the 1993 guidance issued by the Office of Generic Drugs to also require controlled-release generic products to be bioequivalent under steady-state conditions [13].

For controlled-release formulations marketed in multiple strengths, a

Copyright © 2003 Marcel Dekker, Inc.

single-dose BE study under fasting conditions is required only on the highest strength, provided that the compositions of the lower strengths are proportional to that of the highest strength, and all strengths are manufactured under the same conditions. Single-dose BE studies may be waived for the lower strengths on the basis of acceptable dissolution profiles. For controlled-release products that are not compositionally proportional, a single-dose BE study is required for each strength. This requirement can also be waived in the presence of an IVIVC whose predictability has been established. For the waiver to be granted on the basis of an acceptable IVIVC, the following conditions have to be met:

Have the same release mechanism.
Have similar in vitro dissolution profiles.
Are manufactured using the same type of equipment, the same process, and at the same site as other strengths that have bioavailability data.

In addition, one of the following situations should exist:

BE has been established for all strengths of the reference listed product.
Dose proportionality has been established for the reference listed product, and all reference product strengths are compositionally proportional, have the same release mechanism, and the in vitro dissolution profiles for all strengths are similar.
BE is established between the generic product and the reference listed product at the highest and lowest strengths, and for the reference listed product, all strengths are compositionally proportional or qualitatively the same, have the same release mechanism, and the in vitro dissolution profiles are similar.

The criteria for granting such waivers is that the difference in predicted means of C_{max} and AUC is no more than 10% based on dissolution profiles of the highest-strength and the lower-strength product [14].

VIII. SCALE-UP AND POSTAPPROVAL CHANGES FOR MODIFIED-RELEASE FORMULATIONS

In September 1997, the FDA issued a guidance on scale-up and postapproval changes for MR formulations. The purpose of the guidance was to provide recommendations for sponsors of NDAs and ANDAs on the type of information needed for components and composition changes, scale-up and scale-down changes, site of manufacture changes, and process and equipment manufacturing changes [15]. The guidance also improved the consistency of the review process by making the requirements uniform across the reviewing divisions within the FDA.

For each type of change the guidance defines three levels. A Level I change

Copyright © 2003 Marcel Dekker, Inc.

Table 1 Summary of the Requirements for the Levels of Changes in Release-Controlling Components and Composition for Extended-Release Dosage Forms

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	5% W/W change based on total release-controlling excipient (e.g., controlled release polymer, plasticizer) content No other changes	All drugs	Stability Application/compendial requirements No biostudy	Annual report
II	Change in technical grade and/or specifications 10% W/W change based on total release-controlling excipient (e.g., controlled release polymer, plasticizer) content No other changes	Nonnarrow	Notification and updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Prior approval supplement
		Narrow	Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement
III	10% W/W change based on total release-controlling excipient (e.g., controlled release polymer, plasticizer) content	All drugs	Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[b]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 2 Summary of the Requirements for the Levels of Changes in Non-Release-Controlling Components and Composition for Extended-Release Dosage Forms

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	Complete or partial deletion of color/flavor Change in inks, imprints Up to SUPAC-IR level 1 excipient ranges No other changes	All drugs	Stability Application/compendial requirements No biostudy	Annual report
II	Change in technical grade and/or specifications Higher than SUPAC-IR level 1 but less than level 2 excipient ranges No other changes	All drugs	Notification & updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Prior approval supplement
III	Higher than SUPAC-IR level 2 excipient ranges	All drugs	Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 3 Summary of the Requirements for the Levels of Changes in Equipment for Extended-Release Dosage Forms

Level	Classification	Change	Test documentation	Filing documentation
I	Equipment changes No other changes (All drugs)	Alternate equipment of same design and principle Automated equipment	Updated batch record Stability Application/compendial requirements No biostudy	Annual report
II	Equipment changes No other changes (All drugs)	Change to equipment of a different design and operating principle	Updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 4 Summary of the Requirements for the Levels of Changes in Manufacturing Site for Extended-Release Dosage Forms

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	Single facility Common personnel No other changes	All drugs	Application/compendial requirements No biostudy	Annual report
II	Same contiguous campus Common personnel No other changes	All drugs	Identification and description of site change, and updated batch record Notification of site change Stability Application/compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Changes being effected supplement
III	Different campus Different personnel	All drugs	Notification of site change Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 5 Summary of the Requirements for the Levels of Changes in Manufacturing Process for Extended-Release Dosage Forms

Level	Classification	Change	Test documentation	Filing documentation
I	Processing changes affecting the non-release controlling excipients and/or the release controlling excipients No other changes	Adjustment of equipment operating conditions (e.g. mixing times, operating speeds, etc.) Within approved application ranges	Updated batch record Application/compendial requirements No biostudy	Annual Report
II	Processing changes affecting the non-release controlling excipients and/or the release controlling excipients No other changes	Adjustment of equipment operating conditions (e.g., mixing times, operating speeds, etc.) Beyond approved application ranges	Updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in three other media (e.g. water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until 80% of drug released or an asymptote is reached[b] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Changes being effected supplement
III	Processing changes affecting the non-release controlling excipients and/or the release controlling excipients	Change in the type of process used (e.g., from wet granulation to direct compression)	Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 6 Summary of the Requirements for the Levels of Changes in Scale-up/Scale-down for Extended-Release Dosage Forms

Level	Classification	Change	Test documentation	Filing documentation
I	Scale-up of bio-batch(s) or pivotal clinical batch(s) No other changes	−10X (All drugs)	Updated batch record Stability Application/compendial requirements No biostudy	Annual report
II	Scale-up of bio-batch(s) or pivotal clinical batch(s) No other changes	>10X (All drugs)	Updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in three other media (e.g., water, 0.1N HCL, and USP buffer media at pH 4.5 and 6.8) until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Changes being effected supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 7 Summary of the Requirements for the Levels of Changes in Scale-up/Scale-down for Delayed-Release Dosage Forms

Level	Classification	Change	Test documentation	Filing documentation
I	Scale-up of bio-batch(s) or pivotal clinical batch(s) No other changes	−10X (All drugs)	Updated batch record Stability Application/compendial requirements No biostudy	Annual report
II	Scale-up of bio-batch(s) or pivotal clinical batch(s) No other changes	>10X (All drugs)	Updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Changes being effected supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 8 Summary of the Requirements for the Levels of Changes in Manufacturing Site for Delayed-Release Dosage Forms

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	Single facility Common personnel No other changes	All drugs	Application/compendial requirements No biostudy	Annual report
II	Same contiguous campus Common personnel No other changes	All drugs	Identification and description of site change, and updated batch record Notification of site change Stability Application/compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Changes being effected supplement
III	Different campus Different personnel	All drugs	Notification of site change Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 9 Summary of the Requirements for the Levels of Changes in Non-Release-Controlling Components and Composition for Delayed-Release Dosage Forms

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	Complete or partial deletion of color/flavor Change in inks, imprints Upto SUPAC-IR level 1 excipient ranges No other changes	All drugs	Stability Application/compendial requirements No biostudy	Annual report
II	Change in technical grade and/or specifications Higher than SUPAC-IR level 1 but less than level 2 excipient ranges No other changes	All drugs	Notification and updated batch record Stability Application/compendial requirements plus multipoint dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Prior approval supplement
III	Higher than SUPAC-IR level 2 excipient ranges	All drugs	Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 10 Summary of the Requirements for the Levels of Changes in Equipment for Delayed-Release Dosage Forms

Level	Classification	Change	Test documentation	Filing documentation
I	Equipment changes No other changes (All drugs)	Alternate equipment of same design and principle Automated equipment	Updated batch record Stability Application/compendial requirements No biostudy	Annual report
II	Equipment changes No other changes (All drugs)	Change to equipment of a different design and operating principle	Updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 11 Summary of the Requirements for the Levels of Changes in Manufacturing Process for Extended-Release Dosage Forms

Level	Classification	Change	Test documentation	Filing documentation
I	Processing changes affecting the non-release controlling excipients and/or the release controlling excipients No other changes	Adjustment of equipment operating conditions (e.g. mixing times, operating speeds, etc.) Within approved application ranges	Updated batch record Application/compendial requirements No biostudy	Annual report
II	Processing changes affecting the non-release controlling excipients and/or the release controlling excipients No other changes	Adjustment of equipment operating conditions (e.g. mixing times, operating speeds, etc.) Beyond approved application ranges	Updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until 80% of drug released or an asymptote is reached Apply some statistical test (F2 test) for comparing dissolution profiles[a] No biostudy	Changes being effected supplement
III	Processing changes affecting the non-release controlling excipients and/or the release controlling excipients	Change in the type of process used (e.g. from wet granulation to direct compression)	Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[b]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

Table 12 Summary of the Requirements for the Levels of Changes in Release-Controlling Components and Composition for Extended-Release Dosage Forms

Level	Classification	Therapeutic range	Test documentation	Filing documentation
I	−5% W/W change based on total release-controlling excipient (e.g., controlled release polymer, plasticizer) content No other changes	All drugs	Stability Application/compendial requirements No biostudy	Annual report
II	Change in technical grade and/or specifications −10% W/W change based on total release-controlling excipient (e.g., controlled release polymer, plasticizer) content No other changes	Nonnarrow	Notification & updated batch record Stability Application/compendial requirements plus multi-point dissolution profiles in additional buffer stage testing (e.g., USP buffer media at pH 4.5–7.5) under standard and increased agitation conditions until 80% of drug released or an asymptote is reached[a] Apply some statistical test (F2 test) for comparing dissolution profiles[b] No biostudy	Prior approval supplement
		Narrow	Updated batch record Stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement
III	>10% W/W change based on total release-controlling excipient (e.g., controlled release polymer, plasticizer) content	All drugs	Updated batch record & stability Application/compendial (profile) requirements Biostudy or IVIVC[a]	Prior approval supplement

[a] In the presence of an established in vitro/in vivo correlation only application/compendial dissolution testing should be performed.
[b] In the absence of an established in vitro/in vivo correlation.

Copyright © 2003 Marcel Dekker, Inc.

is defined as a change that is unlikely to have any detectable impact on formulation quality and performance and is usually reported in the annual report. A Level II change could have a significant impact on formulation quality and performance and is usually reported in a change-being-affected supplement. A Level III change is likely to have a significant impact on quality and performance and is usually included in a prior-approval supplement.

Tables 1–12 summarize the level for each type of change along with the regulatory requirements for each level of change for both extended- and delayed-release formulations.

Where the "Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Post-approval changes: Chemistry, Manufacturing, and Controls, Invitro Dissolution Testing, and Invivo Bioequivalence Documentation" [14] recommends a biostudy, biowaivers for the same changes made on lower strengths are possible without an IVIVC if:

1. All strengths of the tablets are compositionally proportional or qualitatively the same.
2. In vitro dissolution profiles of all strengths are similar.
3. All strengths have the same release mechanism.
4. Bioequivalence has been demonstrated on the highest strength (comparing changed and unchanged drug product) and the dissolution profiles of the changed and unchanged product are similar in three media (0.1N HCl, phosphate buffer pH 4.5 and 6.8). For beaded capsule formulations the comparability of the dissolution profiles should only be established in the approved dissolution method using the approved dissolution medium.

IX. IN VITRO DISSOLUTION FOR MODIFIED-RELEASE FORMULATIONS

A. IVIVC

Since the release of the drug is the rate-limiting step of the appearance of the drug in the systemic circulation for controlled-release formulations, it is therefore possible to establish a relationship between the in vitro dissolution of the drug and its in vivo performance. A USP PF stimuli article published in 1988 [16] established three levels of correlations:

Level A correlation is defined as a point-to-point relationship between the in vitro dissolution profile and the in vivo input rate (usually expressed as the fraction of drug absorbed versus time). This type of correlation is considered to be the most useful from a regulatory point of view.

Level B correlation: uses the principles of statistical moment analysis. In

Copyright © 2003 Marcel Dekker, Inc.

such a correlation, for example, the mean in vitro dissolution time is correlated with the mean residence time or the mean absorption time in vivo. Such a correlation suffers from the fact that a number of different in vivo profiles can produce the same mean absorption time in vivo. Thus, Level B correlations are considered of little value from a regulatory point of view.

Level C correlation: establishes a relationship between the amount of drug dissolved at a certain time with a certain pharmacokinetic parameter. A multiple Level C correlation, on the other hand, relates one or more PK parameter(s) such as AUC or C_{max} to the amount of drug dissolved at several time points of the dissolution profile.

In September 1997, the FDA issued a guidance on this topic to provide recommendations for the development, evaluation, and applications of IVIVCs.

1. Development of IVIVC

Human data should be utilized for regulatory consideration of an IVIVC. Bioavailability studies for IVIVC development should be performed with enough subjects to characterize adequately the performance of the drug product under study. Although crossover studies are preferred, parallel studies or cross-study analyses may be acceptable. The reference product in developing an IVIVC may be an intravenous solution, an aqueous oral solution, or an IR product. IVIVCs are usually developed in the fasted state. When a drug is not tolerated in the fasted state, studies may be conducted in the fed state. Any in vitro dissolution method may be used to obtain the dissolution characteristics of the oral controlled-release dosage form but the same system should be used for all formulations tested [17]. The preferred dissolution apparatus is USP apparatus I (basket) or II (paddle), used at compendially recognized rotation speeds (e.g., 100 rpm for the basket and 50–75 rpm for the paddle). In other cases, the dissolution properties of some oral controlled-release formulations may be determined with USP apparatus III (reciprocating cylinder) or IV (flow through cell). An aqueous medium, either water or a buffered solution preferably not exceeding pH 6.8, is recommended as the initial medium for development of an IVIVC. For poorly soluble drugs, addition of surfactant (e.g., 1% sodium lauryl sulfate) may be appropriate [18–20].

IVIVCs are established in two stages. First, the relationship between dissolution characteristics and bioavailability characteristics needs to be determined. Second, the reliability of this relationship must be tested. The first stage may be thought of as developing an IVIVC, whereas the second stage may involve evaluation of predictability. The most commonly seen process for developing a Level A IVIVC is to:

Copyright © 2003 Marcel Dekker, Inc.

1. Develop formulations with different release rates, such as slow, medium, fast, or a single release rate if dissolution is condition independent.
2. Obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations.
3. Estimate the in vivo absorption or dissolution time course using an appropriate deconvolution technique for each formulation and subject (e.g., Wagner-Nelson, numerical deconvolution) [21]. These three steps establish the IVIVC model. Alternative approaches to developing Level A IVIVCs are possible. The IVIVC relationship should be demonstrated consistently with two or more formulations with different release rates to result in corresponding differences in absorption profiles. Exceptions to this approach (i.e., use of only one formulation) may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH) [22].

The in vitro dissolution methodology should adequately discriminate among formulations. Dissolution testing can be carried out during the formulation screening stage using several methods. Once a discriminating system is developed, dissolution conditions should be the same for all formulations tested in the bioavailability study for development of the correlation and should be fixed before further steps toward correlation evaluation are undertaken. During the early stages of correlation development, dissolution conditions may be altered to attempt to develop a one-to-one correlation between the in vitro dissolution profile and the in vivo dissolution profile.

Time scaling may be used as long as the time-scaling factor is the same for all formulations [23].

2. Evaluation of an IVIVC

An IVIVC that has been developed should be evaluated to demonstrate that predictability of the in vivo performance of a drug product from its in vitro dissolution characteristics is maintained over a range of in vitro dissolution release rates and manufacturing changes. Since the objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between an in vitro property and a relevant in vivo response, a logical evaluation approach focuses on the estimation of predictive performance or, conversely, prediction error. Depending on the intended application of an IVIVC and the therapeutic index of the drug, evaluation of prediction error internally and/or externally may be appropriate. Evaluation of internal predictability is based on the initial data used to develop the IVIVC model. Evaluation of external predictability is based on additional test data sets.

Copyright © 2003 Marcel Dekker, Inc.

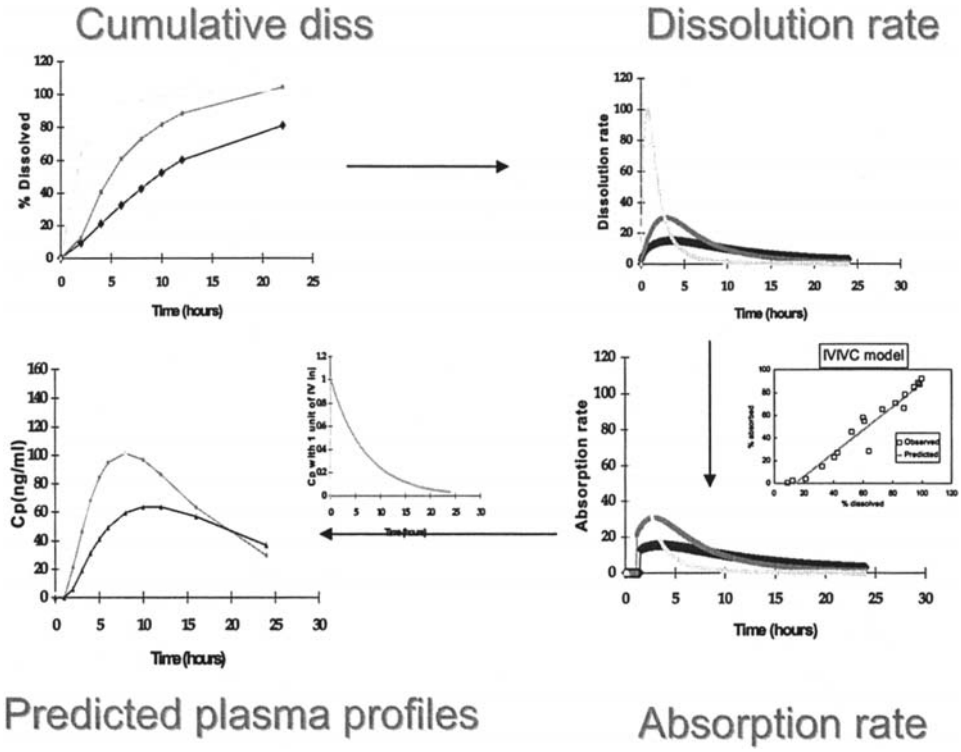


Figure 1 The convolution procedure to predict plasma concentrations from dissolution profiles.

Figure 1 shows the procedure by which one predicts the plasma concentration time profile of an MR formulation from its in vitro dissolution [24].

The dissolution profiles are fitted to a mathematical function. The cumulative dissolution profiles are converted to dissolution rates by taking the first derivative of this function. The dissolution rate is then converted into an absorption rate by using the IVIVC relationship. The predicted plasma concentrations are then obtained by convolving the absorption rates with the disposition function of the drug.

For internal predictability, the IVIVC is deemed acceptable if the average prediction error for all the formulations used to develop the correlation for C_{max} and AUC is less than 10% with none exceeding 15%. If the criteria for internal predictability are not met, then one would proceed to the evaluation of external predictability. If the prediction errors are less than 10%, the IVIVC is deemed

Copyright © 2003 Marcel Dekker, Inc.

acceptable; if the prediction errors are more than 15% on average, the IVIVC is deemed inconclusive and further evaluation would be needed. This can be accomplished by attempting to predict additional data sets. If the prediction errors are on average above 20%, the IVIVC is considered to be of poor predictive ability and is considered unacceptable from a regulatory point of view [14].

3. Applications of IVIVCs

Once a predictive IVIVCs has been developed, in vitro dissolution can not only serve as an important tool for (a) providing process control and quality assurance and (b) determining stable release characteristics over time and facilitating the determination of the effect of minor formulation changes on the release characteristics of the drug product, but can also serve as a surrogate for the in vivo performance of the product. This will in turn reduce the regulatory burden on the industry by reducing the number of studies required for the approval and maintenance on the market of a controlled-release product.

With an IVIVC, waivers for more significant changes are possible. A biowaiver will likely be granted for an oral controlled-release drug product using an IVIVC for:

1. Level 3 process changes as defined in SUPAC-MR.
2. Complete removal of, or replacement of, non-release-controlling excipients as defined in SUPAC-MR.
3. Level 3 changes in the release-controlling excipients as defined in SUPAC-MR.
4. Level 3 site change.

The criteria for granting an in vivo BA/BE waiver are that the predicted mean C_{max} and AUC for the test and reference formulation should differ by no more than 20% as illustrated in Figure 2 [25].

If an IVIVC is developed with the highest strength, waivers for changes made on the highest strength and any lower strengths may be granted if these strengths are compositionally proportional or qualitatively the same, the in vitro dissolution profiles of all the strengths are similar, and all strengths have the same release mechanism.

This biowaiver is applicable to strengths lower than the highest strength, within the dosing range that has been established to be safe and effective, provided the new strengths are compositionally proportional or qualitatively the same, have the same release mechanism, have similar in vitro dissolution profiles, and are manufactured using the same type of equipment, and the same process at the same site as other strengths that have BA data available.

Certain changes generally always necessitate in vivo BA testing and in some cases might necessitate clinical trials, even in the presence of an IVIVC.

Copyright © 2003 Marcel Dekker, Inc.

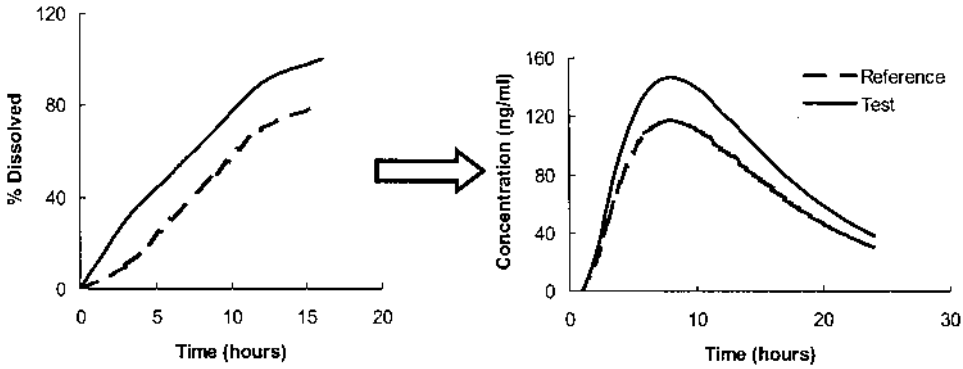


Figure 2 Criteria for granting biowaivers based on a Level A IVIVC.

These include the approval of a new formulation of an approved oral controlled-release drug product when the new formulation has a different release mechanism, approval of a dosage strength higher or lower than the doses that have been shown to be safe and effective in clinical trials, approval of another sponsor's oral controlled-release product even with the same release-controlling mechanism, and approval of a formulation change involving a non-release-controlling excipient in the drug product that may significantly affect drug absorption.

B. Setting Dissolution Specifications

1. No IVIVC Present

The dissolution test is an important tool from a quality control point of view. In the past, the dissolution specifications were set based on the performance of the clinical/bio lots. Therefore, if the release characteristics of the formulation were variable and not well controlled, then one would end up with dissolution specifications that are somewhat wider than a formulation with good release characteristics. The end result of this practice was the possibility of the introduction on the market of potentially highly variable formulations with different in vivo performance. This might result in widely fluctuating plasma concentration profiles leading to a variable therapeutic effect and increased incidence of adverse effects and therapeutic failures. The FDA guidance attempted to change this less than optimal practice. The FDA guidance stipulates that the maximum allowable width of a dissolution specifications be no more than 20% $\pm$ 10% deviation from the dissolution profile of the desired target formulation (see Fig. 3).

The guidance recommends that the dissolution specifications include at least three time points, one covering the initial part of the profile, the second one

Copyright © 2003 Marcel Dekker, Inc.

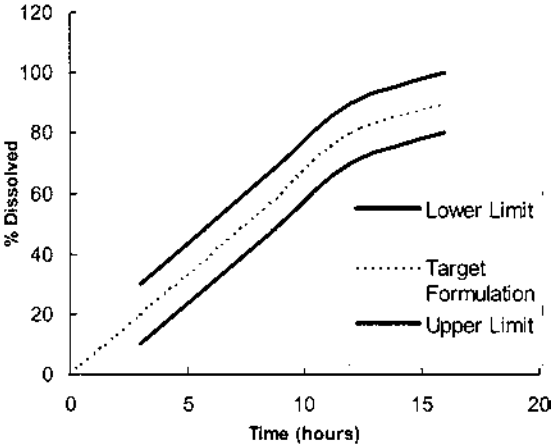


Figure 3 Dissolution specifications in the absence of IVIVC.

the middle part, and the last one the time when 80% dissolution has occurred or the plateau has been reached if one is unable to obtain complete dissolution. Specifications should be set to pass USP stage II of testing (based on average data). However, if dissolution specifications wider than 20% are desired, then one would have to conduct a BE study to show that lots at the upper and lower limit of the specifications are bioequivalent [13].

2. Level A IVIVC Present

In the presence of an IVIVC, the criteria are shifted from the in vitro side to the in vivo side. In this case, the IVIVC is used to predict the plasma concentration time profile that corresponds to lots that are on the upper and lower limit of the dissolution specifications.

Acceptable dissolution specification limits are limits that do not result in plasma concentration time profiles that differ by more than 20% in the area under the plasma concentration time (AUC) and peak plasma concentrations (C_{max}) (usually $\pm 10\%$ of the target clinical/bio formulation). Therefore, it is possible to obtain dissolution specification limits that are wider than 20% if the predicted limits do not result in plasma concentration time profiles that are different in their mean predicted C_{max} or AUC by more than 20%. However, the guidance does not penalize sponsors if the 20% width in the limits results in more than a 20% difference in the predicted pharmacokinetic parameters. Tighter limits than the case where no IVIVC is present will be required only if plasma concentration ranges are needed to avoid potentially serious toxicities [26].

Copyright © 2003 Marcel Dekker, Inc.

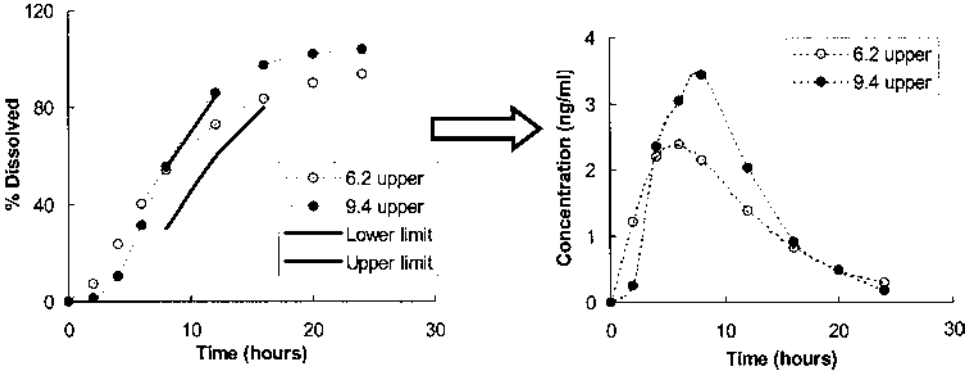


Figure 4 Influence of the release rate specifications on plasma levels: inequivalent plasma profiles.

With a multiple C correlation, the relationship between the amount of drug dissolved at each time point and the relevant PK parameter such as C_{max} and AUC should be used to set the dissolution specification limits in such a way that the upper and lower limit do not result in the release of batches that differ by more than 20% in their plasma concentration time profiles.

3. Release Rate Specifications

The FDA guidance also allows for a novel approach in setting dissolution specifications for formulations exhibiting a zero-order release characteristic.

An example of such a formulation is the osmotic delivery system commonly referred to as gastrointestinal therapeutic systems (GITS). If these formulations are designed to deliver the drug at a constant rate that can be described by a linear relationship over a certain period of time, then one can set a release rate specification to describe the performance of the formulation.

This release rate specification can be in addition to, or instead of, the cumulative dissolution specifications that one usually sets for a modified release product.

Having a release rate specification will provide for better control of the in vivo performance of the drug because it is the release characteristics of the formulation that will determine the rate of appearance in the systemic circulation. This can be described more appropriately by the release rate compared to the cumulative amounts of drug dissolved at a certain interval of time.

As an illustration of this point, consider the dissolution profiles of two lots of the same formulation (shown in Fig. 4) with similar release rates but which

Copyright © 2003 Marcel Dekker, Inc.

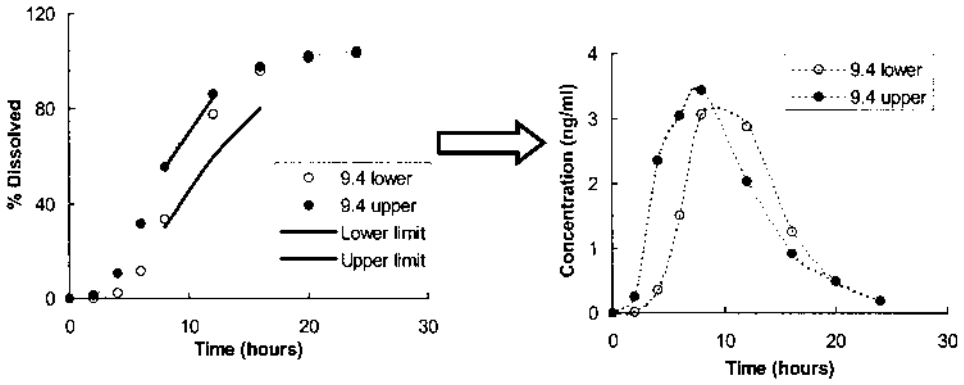


Figure 5 Influence of the release rate specifications on plasma levels: equivalent plasma profiles.

are on the upper and lower limits of the cumulative dissolution specifications. Assuming a Level A correlation for this product, the predicted plasma concentration time profiles corresponding to these two lots are similar, differing only in the time to achieve peak plasma concentration.

On the other hand, if one examines the case presented in Figure 5 whereby the two lots are very close in their cumulative dissolution profiles (both at the upper limit of the dissolution specifications) but are markedly different in their release rates, one can clearly see that the predicted plasma profiles corresponding to these lots are very different and considered not to be bioequivalent.

X. CONCLUSION

The current increase in the number of controlled-release formulations available on the market is the result of the recent advances in drug delivery technologies as well as the availability of sensitive analytical assays. The establishment and understanding of the relationship between the plasma concentrations and/or input rate and the pharmacodynamic properties of the drug (whether desired or adverse) plays an important role in facilitating the development of such formulations. The use of PK/PD models for certain drug products could alleviate the regulatory burden since it would decrease the number of studies needed for both the understanding of the pharmacokinetic and pharmacodynamic properties of the drug product and its approval. Moreover, the establishment of an IVIVC will enable one to predict the plasma concentration time profile from in vitro dissolution characteristics therefore enabling the dissolution test to act as a surrogate for the

Copyright © 2003 Marcel Dekker, Inc.

bioavailability of the drug product. This will in turn decrease the number of BA/BE studies that are needed for the approval and maintenance of the controlled-release product on the market. In addition, the establishment of a predictive IVIVC will enable one to obtain wider dissolution specifications without compromising on the quality of the in vivo performance of the formulation.

REFERENCES

1. PJ Marroum. Bioavailability/Bioequivalence for Oral Controlled Release Products, Controlled Release Drug Delivery Systems: Scientific and Regulatory Issues, Fifth International Symposium on Drug Development, East Brunswick, NJ, May 15–17, 1997.
2. Guidance on BA and BE studies for orally administered drug products—general considerations. Center for Drug Evaluation and Research, Food and Drug Administration, August 2000.
3. Code of Federal Regulations 21 314.54.
4. Code of Federal Regulations 21 320.25.
5. JP Skelly. Division guidelines for the evaluation of controlled release drug products. Center for Drug Evaluation and Research, Food and Drug Administration, April 1984.
6. C Duarte. Cardizem CD, medical review. Division of Cardio-Renal Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, February 1991.
7. PJ Marroum. Clinical pharmacology and biopharmaceutics review. Center for Drug Evaluation and Research, Food and Drug Administration, June 1991.
8. Guidance for providing clinical evidence of effectiveness for human drug and biological products. Center for Drug Evaluation and Research, Food and Drug Administration, May 1998.
9. Approved Drug Products with Therapeutic Equivalence Evaluations. Center for Drug Evaluation and Research, Food and Drug Administration, 20th ed. 2000, pp. vii–xxi.
10. Draft guidance on the food-effect bioavailability and bioequivalence studies. Center for Drug Evaluation and Research, Food and Drug Administration, October 1997.
11. A El-Tahtawy, A Jackson, T Ludden. Pharm Res 11:1330–1336, 1994
12. Guidance bioavailability and bioequivalence studies for orally administered drug products—general considerations. Center for Drug Evaluation and Research, Food and Drug Administration, October 2000.
13. Guidance for oral extended (controlled) release dosage forms: in vivo bioequivalence and in vitro dissolution testing. Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 1993.
14. H Malinowski, PJ Marroum, R Uppoor, et al. FDA guidance for industry, extended release solid oral dosage forms: development, evaluation and application of in vivo/in vitro correlations. Diss Tech 4:23–32, 1997.
15. Guidance for modified release solid oral dosage forms, scale up and post approval

Copyright © 2003 Marcel Dekker, Inc.

changes: chemistry and controls: in vitro dissolution testing and in vivo bioequivalence documentation. Center for Drug Evaluation and Research, Food and Drug Administration, July 1997.
16. US Pharmacopeia 23. General Information/In vitro and In vivo Evaluation of Dosage Forms, ⟨1088⟩ 1995, pp. 1924–1929.
17. H Malinowski. ER guidance. In: G Amidon, JR Robinson, RL Williams, eds. Scientific Foundations for Regulating Drug Product Quality. Alexandria, VA: AAPS Press, 1997, pp. 259–273.
18. M Siewert. Perspectives of in vitro dissolution tests in establishing in vivo in vitro correlations. Eur J Drug Metab Pharmacokin 18:7–18, 1993.
19. JP Skelly, GF Shiu. In vitro/in vivo correlations in biopharmaceutics: scientific and regulatory implications. Eur J Drug Metab Pharmacokin 18:121–129, 1993.
20. HH Blume, I McGilvery, KK Midha. Eur J Pharm Sci 3:113–124, 1995.
21. J Wagner. Absorption analysis and bioavailability. In: J Wagner, ed. Pharmacokinetics for the Pharmaceutical Scientist. Lancaster, PA: Technomic Publishing Company, 1993, pp. 159–205.
22. PJ Marroum. Development of in vivo in vitro correlations, SUPAC-MR/IVIVC guidance FDA training program manual. Center for Drug Evaluation and Research, Food and Drug Administration, July 1997, pp. 62–76.
23. D. Brockmeier, D. Voegele, HM Hattingberg. In vitro–in vivo correlations, a time scaling problem? Drug Res 33:598–601, 1983.
24. R Uppoor. Evaluation of predictability of in vitro in vivo correlations, SUPAC-MR/IVIVC guidance FDA training program manual. Center for Drug Evaluation and Research, Food and Drug Administration, July 1997, pp. 97–110.
25. PJ Marroum. Regulatory examples: dissolution specifications and bioequivalence product standards. In: G Amidon, JR Robinson, RL Williams, eds. Scientific Foundations for Regulating Drug Product Quality. Alexandria VA: AAPS Press, 1997, pp. 305–319.
26. PJ Marroum. Role of in vivo–in vitro correlations in setting dissolutions specifications. Am Pharm Rev 2:39–42, 1999.

Copyright © 2003 Marcel Dekker, Inc.